(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 May 2001 (31.05.2001)

PCT

(10) International Publication Number
WO 01/38564 A2

(51) International Patent Classification[7]: C12Q 1/68, A61P 43/00

(21) International Application Number: PCT/CA00/01404

(22) International Filing Date:
24 November 2000 (24.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/167,623 26 November 1999 (26.11.1999) US

(71) Applicant *(for all designated States except US)*: **MCGILL UNIVERSITY** [CA/CA]; 3550 University Street, Montreal, Quebec H3A 3V9 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ROULEAU, Guy, A.** [CA/CA]; Appartement 7, 4850 Côte Saint-Luc, Montréal, Québec H3W 2H2 (CA). **LAFRENIERE, Ronald, G.** [CA/CA]; 1264 Osborne Avenue, Verdun, Quebec H4H 1X5 (CA). **ROCHEFORT, Daniel** [CA/CA]; 2134 de Calmar, Laval, Quebec H7M 5T1 (CA). **COSSETTE, Patrick** [CA/CA]; 3550 University Street, Montreal, Quebec H3A 3V9 (CA). **RAGSDALE, David** [CA/CA]; 3550 University Street, Montreal, Quebec H3A 3V9 (CA).

(74) Agents: **DUBUC, Jean, H.** et al.; Goudreau Gage Dubuc, The Stock Exchange Tower, Suite 3400, 800 Place Victoria, P.O. Box 242, Montreal, Quebec H4Z 1E9 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSE OR TREAT EPILEPSY

(57) Abstract: The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three genes mapping to chromosome 2, which show mutations in patients with epilepsy. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA) and to the use thereof to assess, diagnose, prognose or treat epilepsy, to predict an epileptic individual's response to medication and to identify agents which modulate the function of the SCNA. The invention provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. In a particular embodiment, the invention provides a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting this screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity thereof is a compound with the desired therapeutic effect.

WO 01/38564 A2

TITLE OF THE INVENTION

LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSE OR TREAT EPILEPSY

FIELD OF THE INVENTION

The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three loci mapping to chromosome 2, which show a linkage with epilepsy in patients. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA), to variations and mutations in these sequences and to the use thereof to assess, diagnose, prognose or treat epilepsy. The invention also provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders.

BACKGROUND OF THE INVENTION

Epilepsy is one of the most common neurological conditions, occurring in about 1.0% of the general population. The disease is characterised by paroxysmal abnormal electrical discharges in the brain, which lead to transient cerebral dysfunction in the form of a seizure. A seizure is considered partial when the epileptic discharge is limited to part of one brain hemisphere, or generalised when it involves both cerebral hemispheres at the onset. The current classification of the epileptic syndromes rests on two criteria: 1) seizure type which may be generalised or partial at the onset, according to clinical and EEG features; and 2) etiology, which may be idiopathic, cryptogenic and symptomatic. Symptomatic epilepsies have multiple and heterogeneous causes including

brain injury, CNS infection, migrational and metabolic disorders. In the majority (65%) of the patients with either generalised or partial epilepsy, there is no underlying cause (idiopathic) or the cause is though to be hidden or occult (cryptogenic). Also, in the idiopathic epileptic syndromes, there is no evidence of cerebral dysfunction other than the seizure, and the neurological examination is normal. There is now increasing evidence that in this latter group, genetic factors are important, especially for the idiopathic generalised epilepsy (IGE). In a recent study, Berkovic et al (1998) showed a 62% concordance rate in monozygotic twins overall for epilepsy. In this study, a higher concordance rate has been found in the generalised compared to the partial epilepsies, with 76% concordance rate for IGE. Recent studies using molecular genetic approaches have shown that many susceptibility genes for the epilepsies in human involve membrane ion channel and related proteins. These studies include the syndrome of benign familial neonatal convulsions where two loci have been identified [EBN1 on chromosome 20, the KCNQ2 gene (a potassium channel); and EBN2 on chromosome 8, the KCNQ3 gene (also a potassium channel)] (Bievert et al, 1998; Charlier et al, 1998; Singh et al, 1998), as well as autosomal dominant nocturnal frontal lobe epilepsy [ADNFLE - chromosome 20, and the CHRNA4 gene (the neuronal nicotinic acetylcholine receptor alpha 4 subunit)] (Steinlein et al, 1995). More recently, there was a clinical description of a new syndrome (GEFS), which consisted of generalised epilepsy with febrile seizures. According to the current classification of epileptic syndrome, this syndrome would fall in the category of IGE, based on the seizure and electroencaphalographic features. However, febrile seizures were present in all probants with GEFS, and the pattern of inheritance was clearly autosomal dominant, which are not part of the usual IGE phenotype. This unique GEFS syndrome has been shown to be associated with a mutation on the beta-1 subunit of brain voltage-gated sodium channel (SCN1B) gene (Wallace et

al, 1998). In addition, three different groups, including the group of the present inventors, have identified another locus on chromosome 2 in large kindred with this specific syndrome (GEFS). This region contains many candidate genes, including a cluster of alpha subunits of sodium channels (SCNA). Voltage-gated sodium channels play an important role in the generation of action potential in nerve cells and muscle. The alpha subunit (SCNA) is the main component of the channel, and would be sufficient to generate an efficient channel when expressed in cells *in vitro*. In turn, the beta-1 and 2 subunits need an alpha subunit to give an effective channel. The role of these subunits would be to modifiy the kinetic properties of the channel, mainly by fast inactivation of the sodium currents. The mutation found in the GEFS syndrome on the SCN1B gene was shown to reduce the fast inactivation of the sodium channels as compared to a normal SCNB1, when co-expressed with an alpha subunit. It is probable that this could be the mechanism by which the mutation induce an hyperexcitability state in the brain, leading to seizure in humans. Interestingly, the mechanism of action of most of the anticonvulsant drugs is through a reduction of the repetitive firing of neurons, which is also known to be dependent on fast inactivation. These finding make it likely that additional epilepsy genes will be identified by mutations in ion channels.

There thus remains a need to identify whether IGE is caused by a mutation in a sodium channel (SCNA). There also remains a need to assess whether a mutation(s) in SCNA is associated with GEFs. There also remains a need to determine whether a mutation that affects the fast inactivation of a sodium channel, given the particular phenotype of GEFS or IGE, could be linked to a region which includes SCNA genes.

The present invention seeks to meet these and other needs.

The present description refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

In one embodiment, the present invention relates to a genetic assay for determining predisposition to epilepsy.

In another embodiment, the present invention relates to a use of at least one of the loci of the present invention or an equivalent thereof (e.g. a loci in linkage disequilibrium therewith) as a marker for epilepsy and to determine the optimal treatment thereof (e.g. to guide the treatment modalities, thereby optimizing treatment to a particular clinical situation).

Yet in another embodiment, the present invention relates to an assay to screen for drugs for the treatment and/or prevention of epilepsy. In a particular embodiment, such assays can be designed using cells from patients having a known genotype at one of the loci of the present invention. These cells harboring recombinant vectors can enable an assessment of the functionality of the SCN1A, and/or SCN2A and/or SCN3A and a combination thereof. Non-limiting examples of assays that could be used in accordance with the present invention include *cis-trans* assays similar to those described in U.S.P. 4,981,784.

It shall be understood that the determination of allelic variations in at least one of the loci of the present invention can be combined to the determination of allelic variation in other gene/markers linked to a predisposition to epilepsy. This combination of genotype analyses could lead to better diagnosis programs and/or treatment of epilepsy. Non-limiting examples of such markers include SCN1B, EBN1, KCNQ2, EBN2, KCNQ3, ADNFLE and CHRNA4.

In accordance with the present invention, there is therefore provided a method of determining an individual's predisposition to epilepsy, which comprises determining the genotype of at least one locus selected from the group consisting of SCN1A, SCN2A and SCN3A. In one particular embodiment, the present invention provides a method of determining an individual's predisposition to epilepsy, which comprises determining a polymorphism (directly or indirectly by linkage disequilibrium) in a biological sample of an individual and analyzing the allelic variation in at least one of the loci selected from SCN1A, SCN2A and SCN3A, thereby determining an individual's predisposition to epilepsy.

In accordance with the present invention, there is also provided a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity is a compound with this therapeutic effect.

Also provided within the present invention is a compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting the screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene, wherein a test compound which modulates the biological activity is a compound with this therapeutic effect.

SCN1A, SCN2A and SCN3A refers to genes and proteins for Sodium Channel, Neuronal Type I, Alpha Subunit isoforms, and are described at OMIM # 182389 (Online Mendelian Inheritance in Man). These genes are structurally distinct sodium channel alpha-subunit isoforms in brain, also known as brain types I, II and III, respectively. Gene, cDNA and protein sequences for the various isoforms are shown in SEQ ID NOS:1-98.

Numerous methods for determining a genotype are known and available to the skilled artisan. All these genotype determination methods are within the scope of the present invention. In a particular embodiment of a method of the present invention, the determination of the genotype comprises an amplification of a segment of one of the loci selected from the group consisting of SCN1A, SCN2A and SCN3A and in a particularly preferred embodiment, the amplification is carried out using polymerase chain reaction.

In a particular embodiment, a pair of primers is designed to specifically amplify a segment of one of the markers of the present invention. This pair of primers is preferably derived from a nucleic acid sequence of SCN1A, SCN2A or SCN3A or from sequences flanking these genes, to amplify a segment of SCN1A, SCN2A or SCN3A (or to amplify a segment of a loci in linkage disequilibrium with at least one of the loci of the present invention). While a number of primers are exemplified herein, other primer pairs can be designed, using the sequences of the SCN1A, SCN2A and SCN3A nucleic acids molecules described hereinbelow. The same would apply to primer pairs from loci in linkage disequilibrium with the markers of the present invention.

Restriction fragment length polymorphisms can be used to determine polymorphisms at the SCN1A, SCN2A and SCN3A loci (and equivalent loci).

While human SCN1A, SCN2A and SCN3A are preferred sequences (nucleic acid and proteins) in accordance with the present invention, the invention should not be so limited. Indeed, in view of the significant conservation of these genes throughout evolution, sequences from different species, and preferably mammalian species, could be used in the assays of the present invention. One non-limiting example is the rat SCN1A ortholog gene which shows 95% identity with the human SCN1A gene. The significant conservation of the mouse SCN1A gene can also be observed in OMIM (see above).

In order to provide a clear and consistent understanding of terms used in the present description, a number of definitions are provided hereinbelow.

As used herein the term "RFLP" refers to restriction fragment length polymorphism.

The terms "polymorphism", "DNA polymorphism" and the like, refer to any sequence in the human genome which exists in more than one version or variant in the population.

The term "linkage disequilibrium" refers to any degree of non-random genetic association between one or more allele(s) of two different polymorphic DNA sequences, that is due to the physical proximity of the two loci. Linkage disequilibrium is present when two DNA segments that are very close to each other on a given chromosome will tend to remain unseparated for several generations with the consequence that alleles of a DNA polymorphism (or marker) in one segment will show a non-random association with the alleles of a different DNA polymorphism (or marker) located in the other DNA segment nearby. Hence, testing of a marker in linkage desiquilibrium with the polymorphisms of the present invention at the SCN1A, SCN2A and/or SCN3A genes (indirect testing), will give almost the same information as

testing for the SCN1A, SCN2A and SCN3A polymorphisms directly. This situation is encountered throughout the human genome when two DNA polymorphisms that are very close to each other are studied. Linkage disequilibriums are well known in the art and various degrees of linkage disequilibrium can be encountered between two genetic markers so that some are more closely associated than others.

It shall be recognized by the person skilled in the art to which the present invention pertains, that since some of the polymorphisms or mutations herein identified in the SCN1A, SCN2A and/or SCN3A genes can be within the coding region of the genes and therefore expressed, that the present invention should not be limited to the identification of the polymorphisms/mutations at the DNA level (whether on genomic DNA, amplified DNA, cDNA, or the like). Indeed, the herein-identified polymorphisms and/or mutations could be detected at the mRNA or protein level. Such detections of polymorphism identification on mRNA or protein are known in the art. Non-limiting examples include detection based on oligos designed to hybridize to mRNA or ligands such as antibodies which are specific to the encoded polymorphism (i.e. specific to the protein fragment encoded by the distinct polymorphisms).

Nucleotide sequences are presented herein by single strand, in the 5' to 3' direction, from left to right, using the one letter nucleotide symbols as commonly used in the art and in accordance with the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission.

Unless defined otherwise, the scientific and technological terms and nomenclature used herein have the same meaning as commonly understood by a person of ordinary skill to which this invention pertains. Generally, the procedures for cell cultures, infection, molecular biology methods and the like are common methods

used in the art. Such standard techniques can be found in reference manuals such as for example Sambrook et al. (1989, Molecular Cloning- A Laboratory Manual, Cold Spring Harbor Laboratories) and Ausubel et al. (1994, Current Protocols in Molecular Biology, Wiley, New York).

The present description refers to a number of routinely used recombinant DNA (rDNA) technology terms. Nevertheless, definitions of selected examples of such rDNA terms are provided for clarity and consistency.

As used herein, "nucleic acid molecule", refers to a polymer of nucleotides. Non-limiting examples thereof include DNA (i.e. genomic DNA, cDNA, RNA molecules (i.e. mRNA) and chimeras of DNA and RNA. The nucleic acid molecule can be obtained by cloning techniques or synthesized. DNA can be double-stranded or single-stranded (coding strand or non-coding strand [antisense]).

The term "recombinant DNA" as known in the art refers to a DNA molecule resulting from the joining of DNA segments. This is often referred to as genetic engineering.

The term "DNA segment", is used herein, to refer to a DNA molecule comprising a linear stretch or sequence of nucleotides. This sequence when read in accordance with the genetic code, can encode a linear stretch or sequence of amino acids which can be referred to as a polypeptide, protein, protein fragment and the like.

The terminology "amplification pair" refers herein to a pair of oligonucleotides (oligos) of the present invention, which are selected to be used together in amplifying a selected nucleic acid sequence by one of a number of types of amplification processes, preferably a polymerase chain reaction. Other types of amplification processes include ligase chain reaction, strand displacement amplification, or nucleic acid sequence-based amplification, as explained

in greater detail below. As commonly known in the art, the oligos are designed to bind to a complementary sequence under selected conditions.

The nucleic acid (i.e. DNA, RNA or chimeras thereof) for practicing the present invention may be obtained according to well known methods.

Oligonucleotide probes or primers of the present invention may be of any suitable length, depending on the particular assay format and the particular needs and targeted genomes employed. In general, the oligonucleotide probes or primers are at least 12 nucleotides in length, preferably between 15 and 24 molecules, and they may be adapted to be especially suited to a chosen nucleic acid amplification system. As commonly known in the art, the oligonucleotide probes and primers can be designed by taking into consideration the melting point of hydrizidation thereof with its targeted sequence (see below and in Sambrook et al., 1989, Molecular Cloning -A Laboratory Manual, 2nd Edition, CSH Laboratories; Ausubel et al., 1989, in Current Protocols in Molecular Biology, John Wiley & Sons Inc., N.Y.).

The term "DNA" molecule or sequence (as well as sometimes the term "oligonucleotide") refers to a molecule comprised of the deoxyribonucleotides adenine (A), guanine (G), thymine (T) and/or cytosine (C). Sometimes, in a double-stranded form, it can comprise or include a "regulatory element" according to the present invention, as the term is defined herein. The term "oligonucleotide" or "DNA" can be found in linear DNA molecules or fragments, viruses, plasmids, vectors, chromosomes or synthetically derived DNA. As used herein, particular double-stranded DNA sequences may be described according to the normal convention of giving only the sequence in the 5' to 3' direction. Of

course, as very well-known, DNA molecules or sequences are often in single stranded form.

"Nucleic acid hybridization" refers generally to the hybridization of two single-stranded nucleic acid molecules having complementary base sequences, which under appropriate conditions will form a thermodynamically favored double-stranded structure. Examples of hybridization conditions can be found in the two laboratory manuals referred to above (Sambrook et al., 1989, *supra* and Ausubel et al., 1989, *supra*) and are commonly known in the art. In the case of a hybridization to a nitrocellulose filter, as for example in the well known Southern blotting procedure, a nitrocellulose filter can be incubated overnight at 65°C with a labeled probe in a solution containing 50% formamide, high salt (5 x SSC or 5 x SSPE), 5 x Denhardt's solution, 1% SDS, and 100 µg/ml denatured carrier DNA (i.e. salmon sperm DNA). The non-specifically binding probe can then be washed off the filter by several washes in 0.2 x SSC/0.1% SDS at a temperature which is selected in view of the desired stringency: room temperature (low stringency), 42°C (moderate stringency) or 65°C (high stringency). The selected temperature is based on the melting temperature (Tm) of the DNA hybrid. Of course, RNA-DNA hybrids can also be formed and detected. In such cases, the conditions of hybridization and washing can be adapted according to well known methods by the person of ordinary skill. Stringent conditions will be preferably used (Sambrook et al.,1989, *supra*).

Probes of the invention can be utilized with naturally occurring sugar-phosphate backbones as well as modified backbones including phosphorothioates, dithionates, alkyl phosphonates and α-nucleotides and the like. Modified sugar-phosphate backbones are generally taught by Miller, 1988, Ann. Reports Med. Chem. 23:295 and Moran et al., 1987, Nucleic Acids Res., 14:5019. Probes of the invention

can be constructed of either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA), and preferably of DNA.

The types of detection methods in which probes can be used include Southern blots (DNA detection), dot or slot blots (DNA, RNA), and Northern blots (RNA detection). Although less preferred, labeled proteins could also be used to detect a particular nucleic acid sequence to which it binds. More recently, PNAs have been described (Nielsen et al. 1999, Current Opin. Biotechnol. 10:71-75). PNAs could also be used to detect the polymorphisms of the present invention. Other detection methods include kits containing probes on a dipstick setup and the like.

Although the present invention is not specifically dependent on the use of a label for the detection of a particular nucleic acid sequence, such a label might be beneficial, by increasing the sensitivity of the detection. Furthermore, it enables automation. Probes can be labeled according to numerous well known methods (Sambrook et al., 1989, supra). Non-limiting examples of labels include ^{3}H, ^{14}C, ^{32}P, and ^{35}S. Non-limiting examples of detectable markers include ligands, fluorophores, chemiluminescent agents, enzymes, and antibodies. Other detectable markers for use with probes, which can enable an increase in sensitivity of the method of the invention, include biotin and radionucleotides. It will become evident to the person of ordinary skill that the choice of a particular label dictates the manner in which it is bound to the probe.

As commonly known, radioactive nucleotides can be incorporated into probes of the invention by several methods. Non-limiting examples thereof include kinasing the 5' ends of the probes using gamma ^{32}P ATP and polynucleotide kinase, using the Klenow fragment of Pol I of *E. coli* in the presence of radioactive dNTP (i.e. uniformly labeled DNA

probe using random oligonucleotide primers in low-melt gels), using the SP6/T7 system to transcribe a DNA segment in the presence of one or more radioactive NTP, and the like.

As used herein, "oligonucleotides" or "oligos" define a molecule having two or more nucleotides (ribo or deoxyribonucleotides). The size of the oligo will be dictated by the particular situation and ultimately on the particular use thereof and adapted accordingly by the person of ordinary skill. An oligonucleotide can be synthetised chemically or derived by cloning according to well known methods.

As used herein, a "primer" defines an oligonucleotide which is capable of annealing to a target sequence, thereby creating a double stranded region which can serve as an initiation point for nucleic acid synthesis under suitable conditions.

Amplification of a selected, or target, nucleic acid sequence may be carried out by a number of suitable methods. See generally Kwoh et al., 1990, Am. Biotechnol. Lab. 8:14-25. Numerous amplification techniques have been described and can be readily adapted to suit particular needs of a person of ordinary skill. Non-limiting examples of amplification techniques include polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), transcription-based amplification, the Q-beta replicase system and NASBA (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86, 1173-1177; Lizardi et al., 1988, BioTechnology 6:1197-1202; Malek et al., 1994, Methods Mol. Biol., 28:253-260; and Sambrook et al., 1989, *supra*). Preferably, amplification will be carried out using PCR.

Polymerase chain reaction (PCR) is carried out in accordance with known techniques. See, e.g., U.S. Pat. Nos. 4,683,195; 4,683,202; 4,800,159; and 4,965,188 (the disclosures of all three U.S. Patent are incorporated herein by reference). In general, PCR involves, a

treatment of a nucleic acid sample (e.g., in the presence of a heat stable DNA polymerase) under hybridizing conditions, with one oligonucleotide primer for each strand of the specific sequence to be detected. An extension product of each primer which is synthesized is complementary to each of the two nucleic acid strands, with the primers sufficiently complementary to each strand of the specific sequence to hybridize therewith. The extension product synthesized from each primer can also serve as a template for further synthesis of extension products using the same primers. Following a sufficient number of rounds of synthesis of extension products, the sample is analysed to assess whether the sequence or sequences to be detected are present. Detection of the amplified sequence may be carried out by visualization following EtBr staining of the DNA following gel electrophores, or using a detectable label in accordance with known techniques, and the like. For a review on PCR techniques (see PCR Protocols, A Guide to Methods and Amplifications, Michael et al. Eds, Acad. Press, 1990).

Ligase chain reaction (LCR) is carried out in accordance with known techniques (Weiss, 1991, Science 254:1292). Adaptation of the protocol to meet the desired needs can be carried out by a person of ordinary skill. Strand displacement amplification (SDA) is also carried out in accordance with known techniques or adaptations thereof to meet the particular needs (Walker et al., 1992, Proc. Natl. Acad. Sci. USA 89:392-396; and ibid., 1992, Nucleic Acids Res. 20:1691-1696).

As used herein, the term "gene" is well known in the art and relates to a nucleic acid sequence defining a single protein or polypeptide. A "structural gene" defines a DNA sequence which is transcribed into RNA and translated into a protein having a specific amino acid sequence thereby giving rise to a specific polypeptide or protein. It will be readily recognized by the person of ordinary skill, that the nucleic

acid sequence of the present invention can be incorporated into anyone of numerous established kit formats which are well known in the art.

A "heterologous" (i.e. a heterologous gene) region of a DNA molecule is a subsegment of DNA within a larger segment that is not found in association therewith in nature. The term "heterologous" can be similarly used to define two polypeptidic segments not joined together in nature. Non-limiting examples of heterologous genes include reporter genes such as luciferase, chloramphenicol acetyl transferase, beta-galactosidase, and the like which can be juxtaposed or joined to heterologous control regions or to heterologous polypeptides.

The term "vector" is commonly known in the art and defines a plasmid DNA, phage DNA, viral DNA and the like, which can serve as a DNA vehicle into which DNA of the present invention can be cloned. Numerous types of vectors exist and are well known in the art.

The term "expression" defines the process by which a gene is transcribed into mRNA (transcription), the mRNA is then being translated (translation) into one polypeptide (or protein) or more.

The terminology "expression vector" defines a vector or vehicle as described above but designed to enable the expression of an inserted sequence following transformation into a host. The cloned gene (inserted sequence) is usually placed under the control of control element sequences such as promoter sequences. The placing of a cloned gene under such control sequences is often refered to as being operably linked to control elements or sequences.

Operably linked sequences may also include two segments that are transcribed onto the same RNA transcript. Thus, two sequences, such as a promoter and a "reporter sequence" are operably linked if transcription commencing in the promoter will produce an RNA transcript of the reporter sequence. In order to be "operably linked" it is

not necessary that two sequences be immediately adjacent to one another.

Expression control sequences will vary depending on whether the vector is designed to express the operably linked gene in a prokaryotic or eukaryotic host or both (shuttle vectors) and can additionally contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements, and/or translational initiation and termination sites.

Prokaryotic expressions are useful for the preparation of large quantities of the protein encoded by the DNA sequence of interest. This protein can be purified according to standard protocols that take advantage of the intrinsic properties thereof, such as size and charge (i.e. SDS gel electrophoresis, gel filtration, centrifugation, ion exchange chromatography...). In addition, the protein of interest can be purified via affinity chromatography using polyclonal or monoclonal antibodies. The purified protein can be used for therapeutic applications.

The DNA construct can be a vector comprising a promoter that is operably linked to an oligonucleotide sequence of the present invention, which is in turn, operably linked to a heterologous gene, such as the gene for the luciferase reporter molecule. "Promoter" refers to a DNA regulatory region capable of binding directly or indirectly to RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of the present invention, the promoter is bound at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter will be found a transcription initiation site (conveniently defined by mapping with S1 nuclease), as well as protein binding domains (consensus sequences) responsible for the

binding of RNA polymerase. Eukaryotic promoters will often, but not always, contain "TATA" boses and "CCAT" boxes. Prokaryotic promoters contain Shine-Dalgarno sequences in addition to the -10 and -35 consensus sequences.

In accordance with one embodiment of the present invention, an expression vector can be constructed to assess the functionality of specific alleles of the SCN1A, SCN2A and SCN3A sodium channels. Non-limiting examples of such expression vectors include a vector comprising the nucleic acid sequence encoding one of the sodium channels (or part thereof) according to the present invention. These vectors can be transfected in cells. The sequences of the alpha subunit of the sodium channels in accordance with the present invention and their structure-function relationship could be assessed by a number of methods known to the skilled artisan. One non-limiting example includes the use of cells expressing the β-1 and β-2 subunits and the sequence of an alpha subunit in accordance with the present invention. For example, an alpha subunit having a mutation, which is linked to epilepsy, could be compared to a sequence devoid of that mutation, as a control. In such cells, the functionality of the sodium channel could be tested as known to the skilled artisan and these cells could be used to screen for agents which could modulate the activity of the sodium channel. For example, agents could be tested and selected, which would reduce the hyperexcitability state of the sodium channel (e.g. their reduction in fast inactivation). Agents known to the person of ordinary skill as affecting other sodium channels could be tested, for example, separately or in batches. Of course, it will be understood that the SCN1A, SCN2A and/or SCN3A genes expressed by these cells can be modified at will (e.g. by *in vitro* mutagenesis or the like).

As used herein, the designation "functional derivative" denotes, in the context of a functional derivative of a sequence whether a

nucleic acid or amino acid sequence, a molecule that retains a biological activity (either function or structural; e.g. sodium channel function or structure) that is substantially similar to that of the original sequence. This functional derivative or equivalent may be a natural derivative or may be prepared synthetically. Such derivatives include amino acid sequences having substitutions, deletions, or additions of one or more amino acids, provided that the biological activity of the protein is conserved. The same applies to derivatives of nucleic acid sequences which can have substitutions, deletions, or additions of one or more nucleotides, provided that the biological activity of the sequence is generally maintained. When relating to a protein sequence, the substituting amino acid generally has chemico-physical properties which are similar to that of the substituted amino acid. The similar chemico-physical properties include, similarities in charge, bulkiness, hydrophobicity, hydrophylicity and the like. The term "functional derivatives" is intended to include "fragments", "segments", "variants", "analogs" or "chemical derivatives" of the subject matter of the present invention. The genetic code, the chemico-physical characteristics of amino acids and teachings relating to conservative vs. non-conservative mutations are well-known in the art. Non-limiting examples of textbooks teaching such information are Stryer, Biochemistry, 3rd ed.; and Lehninger, Biochemistry, 3rd ed. The functional derivatives of the present invention can be synthesized chemically or produced through recombinant DNA technology. all these methods are well known in the art.

The term "variant" refers herein to a protein or nucleic acid molecule which is substantially similar in structure and biological activity to the protein or nucleic acid of the present invention.

As used herein, "chemical derivatives" is meant to cover additional chemical moieties not normally part of the subject matter of the invention. Such moieties could affect the physico-chemical

characteristic of the derivative (i.e. solubility, absorption, half life, decrease of toxicity and the like). Such moieties are examplified in Remington's Pharmaceutical Sciences (1980). Methods of coupling these chemical-physical moieties to a polypeptide or nucleic acid sequence are well known in the art.

The term "allele" defines an alternative form of a gene which occupies a given locus on a chromosome.

As commonly known, a "mutation" is a detectable change in the genetic material which can be transmitted to a daughter cell. As well known, a mutation can be, for example, a detectable change in one or more deoxyribonucleotide. For example, nucleotides can be added, deleted, substituted for, inverted, or transposed to a new position. Spontaneous mutations and experimentally induced mutations exist. The result of a mutations of nucleic acid molecule is a mutant nucleic acid molecule. A mutant polypeptide can be encoded from this mutant nucleic acid molecule.

As used herein, the term "purified" refers to a molecule having been separated from a cellular component. Thus, for example, a "purified protein" has been purified to a level not found in nature. A "substantially pure" molecule is a molecule that is lacking in all other cellular components.

As used herein, "SCNA biological activity" refers to any detectable biological activity of SCN1A, SCN2A or SCN3A gene or protein (herein sometimes collectively called SCNA genes or SCNA proteins). This includes any physiological function attributable to an SCNA gene or protein. It can include the specific biological activity of SCNA proteins which is efflux of sodium or related ions. This includes measurement of channel properties such as, but not limited to: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels, 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential; and 3) the time course of inactivation. At a larger scale, SCNA biological activity includes transmission of impulses through cells, wherein changes in transmission characteristics caused by modulators of SCNA proteins can be identified. Non-limiting examples of such measurements of these biological activities may be made directly or indirectly, such as through the transient accumulation of ions in a cell, dynamics of membrane depolarization, etc. SCNA biological activity is not limited, however, to these most important biological activities herein identified. Biological activities may also include simple binding or pKa analysis of SCNA with compounds, substrates, interacting proteins, and the like. For example, by measuring the effect of a test compound on its ability to increase or inhibit such SCNA binding or interaction is measuring a biological activity of SCNA according to this invention. SCNA biological activity includes any standard biochemical measurement of SCNA such as conformational changes, phosphorylation status or any other feature of the protein that can be measured with techniques known in the art. Finally, SCNA biological activity also includes activities related to SCNA gene transcription or translation, or any biological activities of such transcripts or translation products.

As used herein, the terms "molecule", "compound", "agent" or "ligand" are used interchangeably and broadly to refer to natural, synthetic or semi-synthetic molecules or compounds. The term "molecule" therefore denotes for example chemicals, macromolecules, cell or tissue extracts (from plants or animals) and the like. Non limiting examples of molecules include nucleic acid molecules, peptides, ligands (including, for example, antibodies and carbohydrates) and pharmaceutical agents. The agents can be selected and screened by a

variety of means including random screening, rational selection and by rational design using for example protein or ligand modelling methods such as computer modelling. The terms "rationally selected" or "rationally designed" are meant to define compounds which have been chosen based on the configuration of the interacting domains of the present invention. As will be understood by the person of ordinary skill, macromolecules having non-naturally occurring modifications are also within the scope of the term "molecule". For example, peptidomimetics, well known in the pharmaceutical industry and generally referred to as peptide analogs can be generated by modelling as mentioned above. Similarly, in a preferred embodiment, the polypeptides of the present invention are modified to enhance their stability. It should be understood that in most cases this modification should not alter the biological activity of the protein. The molecules identified in accordance with the teachings of the present invention have a therapeutic value in diseases or conditions in which sodium transport through the sodium channels is compromised by a mutation (or combination thereof) in one of the genes identified in accordance with the present invention. Alternatively, the molecules identified in accordance with the teachings of the present invention find utility in the development of compounds which can modulate the activity of the alpha subunit sodium channels and/or the action potential in nerve cells and muscles cells (e.g. restore the fast inactivation of the sodium channel to normal levels).

As used herein, agonists and antagonists also include potentiators of known compounds with such agonist or antagonist properties. In one embodiment, modulators of the fast inactivation of the sodium channel in accordance with the present invention can be identified and selected by contacting the indicator cell with a compound or mixture or library of molecules for a fixed period of time.

As used herein the recitation "indicator cells" refers to cells that express at least one sodium channel α subunit (SCNA) according to the present invention. As alluded to above, such indicator cells can be used in the screening assays of the present invention. In certain embodiments, the indicator cells have been engineered so as to express a chosen derivative, fragment, homolog, or mutant of the combination of genotypes of the present invention. The cells can be yeast cells or higher eukaryotic cells such as mammalian cells. In one particular embodiment, the indicator cell would be a yeast cell harboring vectors enabling the use of the two hybrid system technology, as well known in the art (Ausubel et al., 1994, *supra*) and can be used to test a compound or a library thereof. In another embodiment, the *cis-trans* assay as described in USP 4,981,784, can be adapted and used in accordance with the present invention. Such an indicator cell could be used to rapidly screen at high-throughput a vast array of test molecules. In a particular embodiment, the reporter gene is luciferase or beta-Gal.

It shall be understood that the "*in vivo*" experimental model can also be used to carry out an "*in vitro*" assay. For example, cellular extracts from the indicator cells can be prepared and used in an "*in vitro*" test. A non-limiting example thereof include binding assays.

In some embodiments, it might be beneficial to express a fusion protein. The design of constructs therefor and the expression and production of fusion proteins and are well known in the art (Sambrook et al., 1989, *supra*; and Ausubel et al., 1994, *supra*).

Non-limiting examples of such fusion proteins include hemaglutinin fusions and Gluthione-S-transferase (GST) fusions and Maltose binding protein (MBP) fusions. In certain embodiments, it might be beneficial to introduce a protease cleavage site between the two polypeptide sequences which have been fused. Such protease cleavage

sites between two heterologously fused polypeptides are well known in the art.

In certain embodiments, it might also be beneficial to fuse the protein of the present invention to signal peptide sequences enabling a secretion of the fusion protein from the host cell. Signal peptides from diverse organisms are well known in the art. Bacterial OmpA and yeast Suc2 are two non-limiting examples of proteins containing signal sequences. In certain embodiments, it might also be beneficial to introduce a linker (commonly known) between the interaction domain and the heterologous polypeptide portion. Such fusion protein find utility in the assays of the present invention as well as for purification purposes, detection purposes and the like.

For certainty, the sequences and polypeptides useful to practice the invention include without being limited thereto mutants, homologs, subtypes, alleles and the like. It shall be understood that generally, the sequences of the present invention should encode a functional (albeit defective) alpha subunit of sodium channels (SCNA). It will be clear to the person of ordinary skill that whether the SCNA sequence of the present invention, variant, derivative, or fragment thereof retains its function, can be determined by using the teachings and assays of the present invention and the general teachings of the art.

It should be understood that the SCNA protein of the present invention can be modified, for example by *in vitro* mutagenesis, to dissect the structure-function relationship thereof and permit a better design and identification of modulating compounds. However, some derivative or analogs having lost their biological function may still find utility, for example for raising antibodies. These antibodies could be used for detection or purification purposes. In addition, these antibodies could

also act as competitive or non-competitive inhibitor and be found to be modulators of the activity of the SCNA proteins of the present invention.

A host cell or indicator cell has been "transfected" by exogenous or heterologous DNA (e.g. a DNA construct) when such DNA has been introduced inside the cell. The transfecting DNA may or may not be integrated (covalently linked) into chromosomal DNA making up the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transfecting DNA may be maintained on a episomal element such as a plasmid. With respect to eukaryotic cells, a stably transfected cell is one in which the transfecting DNA has become integrated into a chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transfecting DNA. Transfection methods are well known in the art (Sambrook et al., 1989, *supra*; Ausubel et al., 1994 *supra*). The use of a mammalian cell as indicator can provide the advantage of furnishing an intermediate factor, which permits for example the interaction of two polypeptides which are tested, that might not be present in lower eukaryotes or prokaryotes. It will be understood that extracts from mammalian cells for example could be used in certain embodiments, to compensate for the lack of certain factors.

In general, techniques for preparing antibodies (including monoclonal antibodies and hybridomas) and for detecting antigens using antibodies are well known in the art (Campbell, 1984, In "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology", Elsevier Science Publisher, Amsterdam, The Netherlands) and in Harlow et al., 1988 (in: Antibody-A Laboratory Manual, CSH Laboratories). The present invention also provides polyclonal, monoclonal antibodies, or humanized versions

thereof, chimeric antibodies and the like which inhibit or neutralize their respective interaction domains and/or are specific thereto.

From the specification and appended claims, the term therapeutic agent should be taken in a broad sense so as to also include a combination of at least two such therapeutic agents. Further, the DNA segments or proteins according to the present invention could be introduced into individuals in a number of ways. For example, cells can be isolated from the afflicted individual, transformed with a DNA construct according to the invention and reintroduced to the afflicted individual in a number of ways. Alternatively, the DNA construct can be administered directly to the afflicted individual. The DNA construct can also be delivered through a vehicle such as a liposome, which can be designed to be targeted to a specific cell type, and engineered to be administered through different routes.

For administration to humans, the prescribing medical professional will ultimately determine the appropriate form and dosage for a given patient, and this can be expected to vary according to the chosen therapeutic regimen (i.e. DNA construct, protein, cells), the response and condition of the patient as well as the severity of the disease.

Composition within the scope of the present invention should contain the active agent (i.e. molecule, hormone) in an amount effective to achieve the desired therapeutic effect while avoiding adverse side effects. Typically, the nucleic acids in accordance with the present invention can be administered to mammals (i.e. humans) in doses ranging from 0.005 to 1 mg per kg of body weight per day of the mammal which is treated. Pharmaceutically acceptable preparations and salts of the active agent are within the scope of the present invention and are well known in the art (Remington's Pharmaceutical Science, 16th Ed., Mack Ed.). For the administration of polypeptides, antagonists, agonists and the like, the

amount administered should be chosen so as to avoid adverse side effects. The dosage will be adapted by the clinician in accordance with conventional factors such as the extent of the disease and different parameters from the patient. Typically, 0.001 to 50 mg/kg/day will be administered to the mammal.

The present invention also relates to a kit for diagnosing and/or prognosing epilepsy, and/or predicting response to a medication comprising an assessment of a genotype at SCNA loci of the present invention (or loci in linkage disequilibrium therewith) using a nucleic acid fragment, a protein or a ligand, a restriction enzyme or the like, in accordance with the present invention. For example, a compartmentalized kit in accordance with the present invention includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allow the efficient transfer of reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include in one particular embodiment a container which will accept the test sample (DNA protein or cells), a container which contains the primers used in the assay, containers which contain enzymes, containers which contain wash reagents, and containers which contain the reagents used to detect the extension products.

BRIEF DESCRIPTION OF THE DRAWINGS

Having thus generally described the invention, reference will now be made to the accompanying drawings, showing by way of illustration a preferred embodiment thereof, and in which:

Figure 1 shows the IGE candidate region on ch 2q23-q31. Order and distance between markers are according to Gyapay et al., 1994.

Figure 2 shows the PCR primers used for genomic PCR-SSCP of SCN1A;

Figure 3 shows the sequence of the SCN1A mutations found in epilepsy patients;

Figure 4 shows the PCR primers used for genomic PCR-SSCP of SCN2A;

Figure 5 shows the mutation found in epilepsy patients in SCN2A;

Figure 6 shows the PCR primers used for genomic PCR-SSCP of SCN3A; and

Figure 7 shows the mutation found in epilepsy patients in SCN3A.

Sequences are also shown in the Sequence Listing. For example, SEQ ID NO.:1 shows the nucleic acid sequence of the adult form of SCN1A; SEQ ID NO.:2 shows the nucleic acid sequence of the neonatal form of SCN1A; SEQ ID NO.:3 shows the protein sequence of the adult form of SCN1A; SEQ ID NO.:4 shows the protein sequence of the neonatal form of SCN1A; SEQ ID NOS.:5-32 show the genomic sequence of SCN1A; SEQ ID NO.:33 shows the cDNA sequence of the adult form of SCN2A; SEQ ID NO.:34 shows the cDNA sequence of the neonatal form of SCN2A; SEQ ID NO.:35 shows the protein sequence of the adult form of SCN2A; SEQ ID NO.:36 shows the protein sequence of the neonatal form of SCN2A; SEQ ID NOS.:37-64 show the genomic sequence of SCN2A; SEQ ID NO.:65 shows the cDNA sequence of the adult form of SCN3A; SEQ ID NO.:66 shows the cDNA sequence of the neonatal form of SCN3A; SEQ ID NO.:67 shows the protein sequence of

the adult form of SCN3A; SEQ ID NO.:68 shows the protein sequence of the neonatal form of SCN3A; and SEQ ID NOS.:69-98 show the genomic sequence of SCN3A. Rat SCNA1 sequences can be found in GenBank under accession numbers M22253 and X03638.

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of preferred embodiments with reference to the accompanying drawing which is exemplary and should not be interpreted as limiting the scope of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Epilepsy is one of the most common neurological conditions, affecting 1-2% of the general population. Familial aggregation studies have shown an increased risk for epilepsy in relatives of probands with different types of epilepsy, and especially for the idiopathic generalized epilepsies (IGEs). The epilepsy genes identified to date account for a very small proportion of all the epilepsies. In addition, they have been identified in rare syndromes where the pattern of inheritance was clearly Mendelian. This is not the case for the vast majority of epileptic patients, however, where the pattern of inheritance is not compatible with a simple Mendelian model. In fact, most authors consider epilepsy to be the result of a combination of many different genetic and environmental factors, features of a complex trait. While the pattern of inheritance is not mendelian, sporadic IGE cases may be caused by specific mutations in the same genes. Based on this assumption, a large cohort of IGE patients was tested for mutation in the SCNA genes.

In order to localize the gene causing epilepsy in a large family segregating an autosomal dominant form of IGE, 41 family members, including 21 affected individuals, were genotyped. A detailed clinical description of this family has been reported elsewhere (Scheffer

and Berkovic 1997). The majority of patients in this family present a benign epilepsy syndrome occurring in childhood and characterized by frequent generalized tonic-clonic seizures not always associated with fever: a syndrome called febrile seizures plus (FS+). However, several patients presented other types of generalized seizures (GTCS) as well, such as myoclonic seizures and absences (Scheffer and Berkovic 1997). Mean age at onset was 2.2 years and offset was 11.7 years. Neurological examination and intellect were normal in all individuals except one, who had moderate intellectual disability. EEG recordings were normal in most patients. However, in three individuals generalized epileptiform activity was found and four patients had mild or moderate diffuse background slowing. Table 1 shows the different types of seizures found in the 21 patients included in this study.

Table 1. Different types of generalized seizures found in the 21 patients included in the linkage analysis.

Type of seizures	n
Febrile convulsions alone	9
GTCSs[a] + absence seizures	4
GTCSs + myoclonic seizures	1
GTCSs + atonic seizures	1
Solitary afebril GTCS	1
Secondary epilepsy + mental retardation	1
Unwitnessed events	4

[a] GTCS: generalized tonic clonic seizure

A genome wide search examining 190 markers identified linkage of IGE to chromosome (ch) 2 based on an initial positive lod score for marker D2S294 (Z=4.4, (=0). A total of 24 markers were tested on ch 2q in order to define the smallest IGE candidate region. Table 2 shows the two-point lod scores for 17 markers spanning the IGE candidate region. The highest lod score (Zmax=5.29; (=0) was obtained with marker D2S324. Critical recombination events mapped the IGE gene to a 29cM region flanked by markers D2S156 and D2S311, assigning the IGE locus to ch 2q23-q31 (Figure 1). Although the relationship of FS+ with other IGE phenotypes remains unclear, the observation that in this family, several affected individuals have different types of generalized seizures, suggests that seizure predisposition determined by the ch 2q-IGE gene could be modified by other genes and/or environmental factors, to produce different seizure types.

Table 2. Two-point lod-scores for 17 markers localized on ch 2q23-q31.

	Recombination fractions								
Locus	**0**	**0.05**	**0.1**	**0.15**	**0.2**	**0.3**	**0.4**	**Zmax**	**max**
D2S142	0.99	1.94	1.97	1.85	1.68	1.22	0.66	1.98	0.078
D2S284	1.3	1.18	1.06	0.94	0.82	0.57	0.3	1.3	0
D2S306	1.9	2.82	2.74	2.52	2.25	1.6	0.85	2.82	0.057
D2S156	2.15	3.05	2.96	2.73	2.43	1.73	0.93	3.05	0.056
D2S354	4.72	4.26	3.82	3.4	2.97	2.1	1.13	4.72	0
D2S111	5.15	4.71	4.26	3.78	3.29	2.26	1.17	5.15	0
D2S124	3.5	3.2	2.89	2.58	2.26	1.58	0.84	3.5	0
D2S382	4.31	3.93	3.54	3.14	2.74	1.91	1.02	4.31	0
D2S399	0.48	0.4	0.33	0.27	0.22	0.14	0.08	0.48	0
D2S294	4.4	4.04	3.65	3.25	2.84	2	1.07	4.4	0
D2S335	4.76	4.32	3.91	3.51	3.1	2.22	1.21	4.76	0
D2S333	1.42	1.23	1.04	0.87	0.72	0.45	0.22	1.4	0
D2S324	5.29	4.72	4.16	3.63	3.13	2.15	1.14	5.29	0
D2S384	3.85	3.52	3.17	2.82	2.45	1.69	0.89	3.85	0
D2S152	1.9	1.7	1.52	1.36	1.2	0.87	0.48	1.9	0
D2S311	-0.81	1.62	1.66	1.58	1.46	1.11	0.63	1.66	0.085
D2S155	-5.21	0.57	1.12	1.29	1.29	1.04	0.59	1.3	0.17

Haplotypes using 17 markers spanning the IGE candidate region were constructed (data not shown). The centromeric boundary was defined by a recombination event between the markers D2S156 and D2S354; whereas a recombination between the markers D2S152 and D2S311 set the telomeric boundary. These critical recombination events localized the IGE gene to a 29cM region flanked by markers D2S156 and D2S311 (Figure 1).

Over the last four decades, family studies provided two important pieces of evidence supporting the role of genetic factors in determining susceptibility to seizures: 1) familial aggregation studies have shown evidence for an increased risk for epilepsy in relatives of probands with different types of epilepsy. In two studies standardized morbidity ratios for unprovoked seizures in relatives of individuals with idiopathic childhood-onset epilepsy varied from 2.5 to 3.4 in siblings and 6.7 in offspring (Anneger et al. 1982; Ottman et al. 1989); and 2) the presence of higher concordance rates for epilepsy in monozygotic than in dizygotic twins. Different studies showed concordance rates varying from 54 to 11 % in monozygotic twins and 10 to 5% in dizygotic pairs (Inouye 1960; Lennox, 1960; Harvald and Hauge 1965; Corey et al. 1991; Silanpaa et al 1991).

It is now generally accepted that seizure susceptibility probably reflects complex interactions of multiple factors affecting neuronal excitability and that most common genetic epilepsies display familial aggregation patterns that are not explained by segregation of a single autosomal gene (Andermann 1982; Ottman et al. 1995). This of course significantly makes more complex one's ability to isolate genes which predispose or induce epilepsy. However, some specific epileptic syndromes, which aggregate in families, may result from definable monogenic abnormalities. These families present a unique opportunity to

rapidly map genes that play a role in determining predisposition to seizures.

To date, there are a total of six loci (Greenberg et al. 1988; Leppert et al 1989; Lewis et al. 1993; Elmslie et al. 1997; Guipponi et al. 1997; Wallace et al. 1998), for which three genes have been identified in specific IGE syndromes (Bievert et al. 1998; Singh et al. 1998; Wallace et al. 1998). Interestingly, all three genes are ion channels, including a mutation found in the Na+-channel (1 in a Tasmania family with febrile seizures and generalized epilepsy (Wallace et al. 1998). While the candidate interval identified in our kindred remains large, a number of interesting genes map to the region. These include a cluster of Na+ channel genes and K+ channel genes (electronic data base search), as well as the GAD1 gene, which encodes for glutamate decarboxylase, an enzyme involved in the syntheses of γ-aminobutyric acid (GABA) (Bu and Tobin 1994). GABA is one of the major neurotransmitters involved in synaptic inhibition in the central nervous system (Barnard et al. 1987). However, the large size of the candidate interval will require further refinement of the locus prior to the identification of the gene responsible for IGE in the kindred studied herein.

Fifty-three % (9/17) of affected individuals in the large IGE family described herein, who had their seizures classified, had only febrile convulsions. However, 41 % of patients (7/17) presented with different types of generalized seizures. These findings may indicate that, although the predisposition to IGE in this family is determined by a single gene localized on ch2q23-q31, the different types of generalized seizures occurring in the same family may have resulted from interactions among genetic and/or environmental modifiers.

In conclusion, a locus for IGE was mapped on ch 2q23-q31. This locus seems to be associated with a specific IGE syndrome, FS

+. However, the relationship of FS+ with other IGE phenotypes, and the role of the ch 2q locus in other FS+ families and in other forms of IGE are still undetermined.

Having identified a locus for IGE on chromosome 2q23-q31, it was next verified whether mutations and/or polymorphisms could be linked to epilepsy. Public data bases were screened to identify potential genes in that chromosome region. The blasts of the data bases were also oriented to identify more specifically, membrane channels since seizures in mice and human are known to be associated with membrane channels. Having identified membrane channel coding sequences or parts thereof by the computer searches, the candidate genes, potentially involved in epilepsy, had to be validated as susceptibility genes for the disease. Two approaches were used. The first one was to test the candidate genes for mutations in a family comprising members having the disease (data not shown). The second approach was as follows. Since it is known that epilepsy results from a lower seizure threshold, and that generalized epilepsy results, in many instances, from a generalized lowering of the seizure threshold, the following hypothesis was formulated. The gene which results in epilepsy in the large family (that enabled the focusing chromosome 2q23-q31) should have other, less severe, mutations that would cause epilepsy in people who have only a weak family history of epilepsy. The sodium channel genes were chosen because they are involved in key electrical functions and could thus be good candidates. To formally test the hypothesis, many (60 to 70) unrelated cases of epilepsy were tested for mutations in these candidate genes. Surprisingly, mutations were found in all three candidate genes.

In order to assess whether mutations/polymorphisms could be identified and correlated to epilepsy, a panel of 70 to 80 epileptic patients (IGE) were tested for mutations in SCN1A, SCN2A and SCN3A,

using Single-strand conformation polymorphism (SSCP). SSCP analysis enables the detection of mutations as small as single-base substitutions. Indeed, such substitutions, by altering the conformations of single-strand DNA molecules, affect the electrophoretic mobilities thereof in non-denaturing gels. Thus, one can distinguish among sequences by comparing the mobilities of wild type (wt), mutant DNA, or different alleles of a given locus. The identification of single base substitutions of genes using SSCP is well known in the art, and numerous protocols are available therefor. A non-limiting example thereof includes fluorescence-based SSCP analysis, following PCR carried out using fluorescent-labeled primers specific for the DNA regions one wishes to amplify.

Upon the identification of differences between normal and epileptic mobilities for one of the SCNA loci of the present invention, the amplified fragments were sequenced and the nucleic acid sequences between a normal patient and an epileptic patient (IGE) compared. This comparison enabled the identification of mutations in SCN1A, SCN2A, and SCN3A. To assess, whether this difference in sequence or mutation was significantly associated with the disease, SSCP analysis was performed once again using a large cohort of normal patients. This analysis enabled to show that the mutations identified by SSCP and confirmed by sequence analysis were not present in the large cohort of normal patients tested, thereby showing that the mutaions identified correlated with IGE, for the population tested.

Taken together, these results show that SCN1A, SCN2A and SCN3A are validated genes associated with epilepsy and more specifically with IGE.

This invention now establishes, for the first time, that SCN1A, SCN2A, and SCN3A, is directly responsible for idiopathic generalized epilepsy (IGE) in certain human populations. Further, this

discovery suggests that compounds which modulate the activity of SCN1A, SCN2A and SCN3A may have application far beyond the small groups of families with IGE, and may have applicability for treating many or all forms of epilepsy and related neurological disorders. It is therefore an object of this invention to provide screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. This invention also claims those compounds, the use of these compounds in treating epilepsy and related neurological disorders, and any use of any compounds identified using such a screening assay in treating epilepsy and related neurological disorders.

Generally, high throughput screens for one or more SCN1A, SCN2A or SCN3A (herein collectively called SCNA) sodium channels modulators i.e. candidate or test compounds or agents (e.g., peptides, peptidomimetics, small molecules or other drugs) may be based on assays which measure biological activity of SCNA. The invention therefore provides a method (also referred to herein as a "screening assay") for identifying modulators, which have a stimulatory or inhibitory effect on, for example, SCNA biological activity or expression, or which bind to or interact with SCNA proteins, or which have a stimulatory or inhibitory effect on, for example, the expression or activity of SCNA interacting proteins (targets) or substrates.

Examples of methods available for cell-based assays and instrumentation for screening ion-channel targets are described in the review by Gonzalez et al. (Drug Discov. Today 4:431-439, 1999), and high-throughput screens for ion-channel drugs are described in review by Denyer et al. (Drug Discov. Today 3:323-332, 1998). Such assays include efflux of sodium or related ions that can be measured in a cell line (recombinant or non-recombinant) using fluorescence-based assays using

both sodium indicator dyes and voltage sensing dyes. Preferred assays employ ^{14}C guanidine flux and/or sodium indicator dyes such as SBFI and voltage sensing dyes such as DiBAC. Oxonal dyes such as $DiBAC_4$ are responsive to membrane depolarization. Hyper-polarization results in removal of the dye from the cell by passive diffusion, while depolarization results in concentration of the dye within the cell.

In one embodiment, the invention provides assays for screening candidate or test compounds which interact with substrates of a SCNA protein or biologically active portion thereof.

In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a SCNA protein or polypeptide or biologically active portion thereof.

In one embodiment, an assay is a cell-based assay in which a cell which expresses a SCNA protein or biologically active portion thereof, either natural or recombinant in origin, is contacted with a test compound and the ability of the test compound to modulate SCNA biological activity, e.g., modulation of sodium efflux activity, or binding to a sodium channel or a portion thereof, or any other measurable biological activity of SCNA is determined. Determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the release of a neurotransmitter or other compound, from a cell which expresses SCNA such as a neuronal cell, e.g. a substantia nigra neuronal cell, or a cardiac cell upon exposure of the test compound to the cell. Furthermore, determining the ability of the test compound to modulate SCNA activity can be accomplished by monitoring, for example, the change in current or the change in release of a neurotransmitter from a cell which expresses SCNA upon exposure to a test compound. Currents in cells can be measured using the patch-clamp technique as

described in the Examples below using the techniques described in, for example, Hamill et al. 1981 Pfluegers Arch. 391:85-100. Alternatively, changes in current can be measured by dye based fluorescence assays described below.

Determining the ability of the test compound to modulate binding of SCNA to a substrate can be accomplished, for example, by coupling the SCNA agent or substrate with a radioisotope or enzymatic label such that binding of the SCNA substrate to SCNA can be determined by detecting the labeled SCNA substrate in a complex. For example, compounds (e.g., SCNA agents or substrates) can be labeled with $^{125}1$, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting radio-emission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase or alkaline phosphatase. In these assays, compounds which inhibit or increase substrate binding to SCNA are useful for the therapeutic objectives of the invention.

It is also within the scope of this invention to determine the ability of a compound (e.g. SCNA substrate) to interact with SCNA without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with SCNA without the labeling of either the compound or the SCNA (McConnell H.M.et al. (1992), Science 257:1906-1912). As used herein, a "microphysiometer" (e.g., Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and SCNA.

Modulators of SCNA can also be identified through the changes they induce in membrane potential. A suitable instrument for

measuring such changes is the VIPR™ (voltage ion probe reader) from Aurora Biosciences. This instrument works together with a series of voltage-sensing ion probe assays. The probes sense changes in transmembrane electrical potential through a voltage-sensitive FRET mechanism for which the ratio donor fluorescence emission to acceptor fluorescence emission reveals the extent of cell depolarization for both sodium and potassium channels. Depolarization results from transport of a quencher across the membrane and far enough away from a membrane-boundfluorescence emitter to relieve the initial quenching and produce light at the emission wavelength of the emitter. The system follows fluorescence at two wavelengths, both the intensities and ratios change during cell depolarization. The reader permits detection of sub-second, real-time optical signals from living cells in a microplate format. The system is amenable to manual operation for assay development or automation via robots for high-throughput screening.

In another embodiment, the assay is a cell-based assay comprising a contacting of a cell containing a target molecule (e.g. another molecule, substrate or protein that interacts with or binds to SCNA) with a test compound and determining the ability of the test compound to indirectly modulate (e.g. stimulate or inhibit) the biological activity of SCNAby binding or interacting with the target molecule. Determining the ability of the test compound to indirectly modulate the activity of SCNA can be accomplished, for example, by determining the ability of the test compound to bind to or interact with the target molecule and thereby to indirectly modulate SCNA , to modulate sodium efflux, or to modulate other biological activities of SCNA. Determining the ability of the SCNA protein or a biologically active fragment thereof, to bind to or interact with the target molecule can be accomplished by one of the methods described above or known in the art for determining direct

binding. In a preferred embodiment, determining the ability of the test compound's ability to bind to or interact with the target molecule and thereby to modulate the SCNA protein can be accomplished by determining a secondary activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g. intracellular Ca2+, diacylglycerol, IP3, and the like), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (comprising a target -responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, such as luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter. Alternatively, recombinant cell lines may employ recombinant reporter proteins which respond, either directly or indirectly to sodium efflux or secondary messengers all as known in the art.

In yet another embodiment, an assay of the present invention is a cell-free assay in which a SCNA protein or biologically active portion thereof, either naturally occurring or recombinant in origin, is contacted with a test compound and the ability of the test compound to bind to, or otherwise modulate the biological activity of, the SCNA protein or biologically active portion thereof is determined. Preferred biologically active portions of the SCNA proteins to be used in assays of the present invention include fragments which participate in interactions with non-SCNA molecules, (e.g. other channels for sodium, potassium or Ca+ or fragments thereof, or fragments with high surface probability scores for protein-protein or protein-substrate interactions). Binding of the test compound to the SCNA protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the SCNA protein or biologically active portion thereof

with a known compound which binds SCNA to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a SCNA protein, wherein determining the ability of the test compound to interact with a SCNA protein comprises determining the ability of the test compound to preferentially bind to SCNA or biologically active portion thereof as compared to the known compound.

In another embodiment, the assay is a cell-free assay in which a SCNA protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the SCNA protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished, for example, by determining the ability of the SCNA protein to bind to a SCNA target molecule by one of the methods described above for determining direct binding. Determining the ability of the SCNA protein to bind to a SCNA target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA, Sjolander, S. and Urbaniczky, C. (1991) Anal. Chem. 63:2338-2345 and Szabo et al. (1995) Curr. Opin. Struct. Biol. 5:699- 705). As used herein, "BIA" refers to a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g. BIA core). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

In an alternative embodiment, determining the ability of the test compound to modulate the activity of a SCNA protein can be accomplished by determining the ability of the test compound to modulate the activity of an upstream or downstream effector of a SCNA target

molecule. For example, the activity of the test compound on the effector molecule can be determined or the binding of the effector to SCNA can be determined as previously described.

The cell-free assays of the present invention are amenable to use of both soluble and/or membrane-bound forms of isolated proteins. In the case of cell-free assays in which a membrane-bound form of an isolated protein is used (e.g. a sodium channel) it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the isolated protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n- dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl- N -methylglucamide, Triton® X-IOO, Triton®X-114, Thesit®, Isotridecypoly(ethylene glycol ether)n. 3-[(3- cholamidopropyl)dimethy-amino]-l-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamino]-2-hydroxy-l-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammnonio-l-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either SCNA or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a. test compound to a SCNA protein or interaction of a SCNA protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes and micro-centrifuge tubes. In one embodiment a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example. glutathione-S-transferase/SCNA fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto

glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or SCNA protein and the mixture incubated under conditions conducive to complex formation (e.g. at physiological conditions for salt and pH). Following incubation the beads or microtitre plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of SCNA binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices (and well-known in the art) can also be used in the screening assays of the invention. For example, either a SCNA protein or a SCNA target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated SCNA protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with SCNA protein or target molecules but which do not interfere with binding of the SCNA protein to its target molecule can be derivatized to the wells of the plate, and unbound target or SCNA protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST -immobilized complexes, include immunodetection of complexes using antibodies reactive with the SCNA protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the SCNA protein or target molecule.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate vesicular traffic and protein transport in a cell, e.g. a neuronal or cardiac cell using the assays described in for example Komada M. et al. (1999) Genes Dev.13(11):1475-85, and Roth M.G. et a1. (1999) Chem. Phys. Lipids. 98(12):141-52.

In another preferred embodiment candidate, or test compounds or agents are tested for their ability to inhibit or stimulate or regulate the phosphorylation state of a SCNA channel protein or portion thereof, or an upstream or downstream target protein, using for example an *in vitro* kinase assay. Briefly, a SCNA target molecule (e.g. an immunoprecipitated sodium channel from a cell line expressing such a molecule), can be incubated with radioactive ATP , e.g., [gamma-32P] - ATP , in a buffer containing MgCl2 and MnCl2, e.g., 10 mM MgCl2 and 5 mM MnCl2. Following the incubation, the immunoprecipitated SCNA target molecule (e.g. .the sodium channel), can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, e.g., a PVDF membrane, and autoradiographed. The appearance of detectable bands on the auto radiograph indicates that the SCNA substrate, e.g., the sodium channel, has been phosphorylated. Phosphoaminoacid analysis of the phosphorylated substrate can also be performed in order to determine which residues on the SCNA substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards. Assays such as those described in, for example, Tamaskovic R. et al. (1999) Biol. Chem. 380(5):569-78.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to associate with (e.g. bind) calcium, using for example, the assays described in Liu L. (1999) Cell Signal. 11(5):317-24 and Kawai T. et al. (1999) Oncogene 18(23):3471-80.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate chromatin formation in a cell using for example the assays described in Okuwaki M. et al. (1998) J. Biol. Chem. 273(51):34511-8 and Miyaji- Yamaguchi M. (1999) J. Mol. Biol. 290(2): 547-557.

In yet another preferred embodiment candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cellular proliferation, using for example, the assays described in Baker F.L. et al. (1995) Cell Prolif. 28(1):1-15, Cheviron N. et al. (1996) Cell Prolif. 29(8):437-46. Hu Z. W. et al. (1999) J: Pharmacol. Exp. Ther. 290(1):28-37 and Elliott K. et al. (1999) Oncogene 18(24):3564-73.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to regulate it's association with the cellular cytoskeleton. Using for example, the assays similar to those described in Gonzalez C. et al. (1998) Cell Mol. Biol. 44(7):1117-27 and Chia C.P. et al. (1998) Exp. Cell Res. 244(1):340-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. et al. (1985) J. Biol. Chem. 260(8):4740-4 and Barker J.L. et al. (1984) Neurosci. Lett. 47(3):313-8.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a SCNA molecule's ability to modulate cytokine signaling in a cell, (e.g., a neuronal or cardiac cell), the assays described in Nakashima Y. et al. (1999)J: Bone Joint Surg. Am. 81 (5):603-15.

In another embodiment, modulators of SCNA expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of SCNA mRNA or protein in the cell is determined. The level of expression of SCNA mRNA or protein in the presence of the candidate compound is compared to the level of expression of SCNA mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of SCNA expression based on this comparison. For example, when expression of SCNA mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of SCNA mRNA or protein expression. Alternatively, when expression of SCNA mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of SCNA mRNA or protein expression. The level of SCNA mRNA or protein expression in the cells can be determined by methods described herein or other methods known in the art for detecting SCNA mRNA or protein.

The assays described above may be used as initial or primary screens to detect promising lead compounds for further development. Often, lead compounds will be further assessed in additional, different screens. Therefore, this invention also includes secondary SCNA screens which may involve electrophysiological assays utilizing mammalian cell lines expressing the SCNA channels such as

patch clamp technology or two electrode voltage clamp and FRET-based voltage sensor. Standard patch clamp assays express wild type and mutant channels in *Xenopus* oocytes, and examine their properties using voltage-clamp electrophysiological recording. Wild type sodium channels are closed at hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds.

Tertiary screens may involve the study of the identified modulators in rat and mouse models for epilepsy. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an test compound identified as described herein (e.g., a SCNA modulating agent, an antisense SCNA nucleic acid molecule, a SCNA-specific antibody, or a SCNA-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatment (e.g. treatments of different types of epilepsy or CNS disorders), as described herein.

The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic

library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des. 12: 145, 1997). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA. 90:6909; Erb et al. (1994) Proc. Natl. Acad. Sci. USA 91:11422; Zuckermann et al. (1994), J. Med. Chem. 37:2678; Cho et al. (1993) Science 261 :1303; Carrell et al. (1994) Angew. Chem, Int. Ed Engl. 33:2059; Carell et al. (1994) Angew. Chem. Jnl. Ed. Engl. 33:2061; and in Gallop et al. (1994). Med Chem. 37:1233. Libraries of compounds may be presented in solution (e.g.. Houghten (1992) Biotechniques 13:412-421). or on beads (Lam (199]) Nature 354:82-84), chips (Fodor (1993) Nature 364:555-556). bacteria (Ladner USP 5.223,409), spores (Ladner USP '409), plasmids (Cull et al.(1992) Proc Natl Acad Sci USA 89:1865-1869) or on phage (Scott and Smith (1990); Science 249:386-390). Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) Proc. Natl. Acad. Sci. USA. 90:6909; Erb et al. (1994) Proc. Natl. Acad .Sci. USA 91: 11422; Zuckermann et al. (1994), .J: Med. Chem. 37:2678; Cho et al. (1993), Science 261 :1303; Carrel1 et al. (1994) Angew. Chem Int. Ed. Engl. 33:2059, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

It is recognized by the inventors that certain therapeutic agents have been identified for cardiac, muscular, chronic pain, acute pain and other disorders, and analgesics and anesthetics that are modulators of sodium channels. Use of these sodium channel modulators

for treating epilepsy and related neurological disorders also falls within the scope of this invention. In one embodiment of this invention, sodium channel blockers are modified to achieve improved transport across the blood brain barrier in order to have direct effect on neuronal SCNA proteins and genes. Descriptions of such compounds are found at Hunter, JC et al. Current Opinion in CPNS Invest. Drugs. 1999 1(1):72-81; Muir KW et al. 2000. Cerebrovasc. Disc. 10(6):431-436; Winterer, G. 2000. Pharmacopsychiatry 33(5):182-8; Clare et al. 2000. Drug. Discov. Today 5(11):506-520; Taylor CP et al. 2000. Adv. Pharmacol. 39:47-98, and Pugsley MK et al. 1998. Eur. J. Pharmacol. 342(1)93-104.

It is also recognized by the inventors that compounds which modulate (i.e. either upregulate or downregulate) transcription and translation of SCNA genes are useful for treating epilepsy or related neurological disorders. According to this invention, test compounds which modulate the activity of promoter elements and regulatory elements of sodium channel genes are useful for treating these disorders.

In summary, based on the disclosure herein, those skilled in the art can develop SCNA screening assays which are useful for identifying compounds which are useful for treating epilepsy and other disorders which relate to potentiation of SCNA expressing cells. The assays of this invention may be developed for low-throughput, high-throughput, or ultra-high throughput screening formats.

The assays of this invention employ either natural or recombinant SCNA protein. Cell fraction or cell free screening assays for modulators of SCNA biological activity can use *in situ*, purified, or purified recombinant SCNA proteins. Cell based assays can employ cells which express SCNA protein naturally, or which contain recombinant SCNA gene constructs, which constructs may optionally include inducible promoter sequences. In all cases, the biological activity of SCNA can be

directly or indirectly measured; thus modulators of SCNA biological activity can be identified. The modulators themselves may be further modified by standard combinatorial chemistry techniques to provide improved analogs of the originally identified compounds.

Finally, portions or fragments of the SCNA cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome and thus, locate gene regions associated with genetic disease (mutations/polymorphisms) related to epilepsy or CNS disorders that involve SCNA directly or indirectly; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample.

The present invention is illustrated in further detail by the following non-limiting examples.

EXAMPLE 1

Molecular analysis

Genomic DNA was extracted from blood samples (Sambrook et al. 1989) or lymphoblastoid cell lines (Anderson and Gusella 1984) from each individual. A panel of 210 dinucleotide (CA)n repeat polymorphic markers with high heterozygosity (75%) were chosen from the 1993-94 Généthon map (Gyapay et al. 1994). Dinucleotide markers were spaced an average of 20 cM from each other throughout the 22 autosomes.

Genotyping of microsatellite markers was accomplished by polymerase chain reaction (PCR). The reaction mixture was prepared in a total volume of 13µl, using 80ng genomic DNA; 1.25µl 10x buffer with 1.5mM MgCl2; 0.65µl BSA (2.0mg/ml); 100ng of each

oligonucleotide primer; 200mM dCTP, dGTP and dTTP; 25mM dATP; 1.5mCi [35S] dATP; and 0.5units Taq DNA polymerase (Perkin-Elmer). Reaction samples were transferred to 96 well plates and were subjected to: 35 cycles of denaturation for 30 seconds at 94°C, annealing for 30 seconds at temperatures varying from 55°C to 57°C depending on the specificity of the oligonucleotide primers, and elongation for 30 seconds at 72°C. PCR reaction products were electrophoresed on 6% denaturing polyacrylamide sequencing gels.

EXAMPLE 2

Genetic analysis

Two-point linkage analysis was carried out using the MLINK program version 5.1 from the LINKAGE computer package (Lathrop et al. 1984). Precise values for Zmax were calculated with the ILINK program from the same computer package. Lod scores were generated based on an autosomal dominant mode of inheritance, 80% penetrance, disease gene frequency of 1:500 and allele frequencies for all allele markers calculated from the pedigree using the computer program ILINK (Lathrop et al. 1984).

EXAMPLE 3

Mutations in SCN1A in IGE patients

Genomic DNA form IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 2. Following PCR, SSCP analysis was performed and mutations in SCN1A were identified as follows (Figure 3): (1) Glu1238Asp; normal: GCA TTT GAA GAT ATA; patient R10191 who has an idiopathic generalized epilepsy (IGE): GCA TTT GAC GAT ATA (found in 1 of 70 IGE patients). The mutation is thus a conservative aa

change, in the extracellular domain between III-S1 and III-S2. Furthermore, this residue is located at the junction between the TM domain and the extracellular domain. It may thus influence gating activity. The aa change between adult and neonatal isoforms is at a similar juxta-TM domain position (between I-S3 and I-S4).

(2) Ser1773Tyr; normal: ATC ATA TcC TTC CTG, patient R9049 (affected with IGE): ATC ATA TmC TTC CTG :(TCC>TAC). This mutation is in the middle of IV-S6 TM domain; found in 1/70 IGE patients, and 0/150 control subjects tested. This mutation is interesting from a biological point of view for a number of reasons. First, this region of SCN gene (IV-S6) has been found to play a critical role in fast inactivation of the SCN, by mutagenesis experiments in rat SCN (McPhee et al., 1998). This is highly relevant for pathophysiology of epilepsy, since this may increase neuronal hyperexcitability. Moreover, in patients with GEFs, a mutation has been found in the SCNB1 subunit, causing impairment of the fast inactivation of the SCN (Wallace et al, 1999). Finally, many of the antiepileptic drugs (e.g. phenytoin, carbamazepine) primarly act by reducing the repetivive firing of neuron, which also involves fast inactivation of the SCN.

EXAMPLE 4

Mutations in SCN2A in IGE patients

Genomic DNA form IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 4. Following PCR, SSCP analysis was performed and mutations in SCN2A were identified as follows (Figure 5):

(1) Lys908Arg: normal: TAC AAA GAA for patient numbers always preceded by R; R9782 (Patient with IGE): TAC AGA GAA. The mutation is thus a conservative aa change, located in an extracellular domain

between TM domains IIS5 and IIS6; in 1/70 IGE patients; 0/96 normal controls. The mutation involves an important component of the SCN gene, since the S5 and S6 segments are thought to form the wall of the transmembrane pore which allows the sodium to enter the cell. This may have an influence on the gating control of the pore.

(2) Leu768Val, in individuals R8197, R9062 and R9822 (all IGE patients) (found in 3/70 IGE patients and 0/65 control subjects). The mutations is in the IV-S6 component of the sodium channel, which is important in the inactivation of the channel (see above for more detail).

EXAMPLE 5

Mutations in SCN3A in IGE patients

Genomic DNA from IGE and normal patients was obtained by conventional methods. Primers used to amplify the genomic DNA are shown in Figure 6. Following PCR, SSCP analysis was performed and mutations in SCN3A were identified as follows (Figure 7):

(1) Asn43DEL: allele 1: CAA GAT AAT GAT GAT GAG ; allele 2: CAA GAT --- GAT GAT GAG ; in open reading frame deletes 1 aa: DNDDEN->QDDDEN, in the cytoplasmic N-terminal segment; in IGE patients, the frequency of allele 1 = 131/146 (0.90); allele 2= 15/146 (0.10); for IGE patients: homozygotes (22): R3958, R9632; heterozygotes (12): R9049, R9152, R9649, R9710, R9896, R10069, R10191, R10213, R9993, R10009, R10256 . Of note, 2 patients are homozygous for the rare allele and all patients have IGE. In controls: allele 1 = 145/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes were found.

(2) normal: tggtgtaaggtag, R10670 (IGE patient): tggtataaggtag, in conserved intron between 5N & 5A exons, significance uncertain.

(3) normal: ccccttatatctccaac, R10250 (IGE patient): ccccttatayctccaac; in conserved intron between 5N & 5A exons, significance uncertain.

(4) Val1035Ile: normal: AAA TAC GTA ATC GAT, R9269 (IGE patient): AAA TAC RTA ATC GAT ; (GTA>ATA = Val>Ile). The mutation is thus a conservative aa change which destroys a SnaBI site (this could thus be used as a polymorphism identifiable by restriction enzyme digestion). In SCN1A, this Val is a Ile, therefore probably not a causative mutation. In cytoplasmic domain bw II-S6 & III-S1 TMs; found in 1/70 IGE alleles; and 0/70 controls.

EXAMPLE 6

SCN1A is involved in idiopathic generalized epilepsy

The assumption that SCN1A gene is involved in idiopathic generalised epilepsy in humans is based on many sets of evidence. First, a mutation has been found in a large Australian family with autosomal dominant epilepsy. The phenotype is idiopathic generalised epilepsy that is associated with febrile seizures (GEFS syndrome). The gene for this family has been previously mapped to the long arm of chromosome 2. The maximum lod score is 6.83 for marker D2S111. The candidate region is very large, spanning 21cM between markers D2S156 and D2S311. However, within this interval, there is a cluster of sodium channel genes, including SCN1A which was hypothesized to be a candidate gene for the disease.

Screening by SSCP of a small panel of three (3) affected patients form the family, and 3 normal controls was carried-out at first. All the exons of the SCN1A gene have been amplified by PCR, and a SSCP variant in exon 4 was found for all of the affected individuals, and none of the controls. By sequencing an affected patient and a control, an A-T substitution at nucleotide 565 was found. This variation destroys a BamHI restriction site, this enzyme was thus used as a diagnostic test to

screen all the affected patients from the family, as well as more control cases. All affected patients from the family have A565T substitution, and none of the unaffected patients in the same kindred. An A565T substitution was not found in more than 400 control chromosomes.

The A565T substitution correspond to a non-conservative amino acid change (D188V). This amino acid is conserved in all sodium channels thus far identified, in all species. The only exception is SCN2A identified in rat by Numa et al, where the aspartic acid is replaced by asparagine. However, it is likely that this represents an error during replication of cDNA, since other investigators have cloned the same gene in rat and found that the aspartic acid is conserved at position 188. Moreover, the same group has shown that D188N has a functional effect on channel activation in oocytes (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Of note, this A565T substitution has not been found in 150 epileptic patients and in 200 control patients. Thus, this substitution has yet to be identified after 700 chromosomes assessments.

In view of proving that D188V in SCN1A, identified in the large Australian family studied, is a pathogenic mutation, the oligonucleotide mismatch mutagenesis technique was used to introduce the mutation in rat SCN1A clone. RNA was isolated from mutant and wild-type clones, and injected into oocytes in view of recording sodium currents by the patch-clamp technique. The amplitude of the currents was dramatically reduced for the mutant. Also, a small shift in the inactivation curve was observed for the mutant, as compared to the wild-type. Taken together, these preliminary results confirm a functional effect of D188V mutation on SCN1A gene. (more detail below).

The results presented herein are corroborated by studies from other investigators. For example, several other groups have also found linkage to the same locus on chromosome 2 for families with

GEFS or very similar syndromes. Mutations in SCN1A (Thr875Met mutation; Arg1648His) have been found to be the cause of the epileptic syndrome in at least two (2) of these families (Escayg et al., *Nature Genetics*. 24(4):343-5, 2000). Also, GEFS syndrome has been shown to be caused by mutation in SCN1B gene. It is demonstrated that the beta subunits interact with alpha subunits of voltage-gated sodium channels to alter kinetics of sodium currents in cells. These data suggest a common mechanism for generating abnormal neuronal discharges in the brain of patients with idiopathic generalised epilepsy.

Finally, in the process of screening patients from the large kindred with GEFS described above, a large cohort of patients with idiopathic generalised epilepsy was also screened by SSCP. Two (2) SSCP variants, that were subsequently sequenced were thereby identified. The variation observed are shown in Table 3:

Table 3

exon	DNA variation	IGE alleles	Control alleles
1Ax17	Glu1238Asp; conservative AA change in extracellular domain between III-S1 and III-S2	3/254	0/284
1Ax24.2	Ser1773Tyr; middle of IV-S6 TM domain	1/252	0/334

Previous functional studies have shown that amino acid substitution in the IV-S6 transmembrane domain of SCN2A significantly affects the rate of inactivation of the channel. It is thus likely that Ser1773Tyr will have an effect on the SCN1A gene function. Such functional studies are currently underway.

EXAMPLE 7

Further validation of the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE and epilepsy in general

A number of methods could be used to further validate the role of SCN1A, SCN2A, SCN3A, and specific mutations thereof in IGE. For example, additional patients could be screened for mutations in SCN1A, SCN2A, or SCN3A. Furthermore, additional normal patients could be screened in order to validate that the mutations identified significantly correlate with disease, as opposed to reflecting a polymorphism which is not linked to IGE. Polymorphisms which are not directly linked to IGE, if in linkage disequilibrium with a functional mutation

linked to IGE, could still be useful in diagnosis and/or prognosis assays. In addition, functional studies can be carried. Numerous methods are amenable to the skilled artisan. One particularly preferred functional assay involves the use of Xenopus oocytes and recombinant constructs harboring normal or mutant sequence of SCN1A, SCN2A, or SCN3A. Xenopus oocytes have been used in functional assays to dissect the structure-function relationship of the cyclic AMP-modulated potassium channel using recombinant KCNQ2 and KCNQ3 (Schroeder et al., 1998). As well, it has been used to dissect the structure-function relationship of the beta subunit of the sodium channel (SCN1B gene; Wallace et al. 1998).

One such example of functional studies was investigated by assessing the effects of mutation D188V in the SCN1A gene on sodium channel function by introducing the mutation into a cDNA encoding the rat ortholog SCN1A gene. This rate gene shares > 95% identity with the human SCN1A gene. The expression of wild type and mutant channels in *Xenopus* oocytes, and the examination of their properties using voltage-clamp electrophysiological recording is amenable to this *Xenopus* system. Wild type sodium channels are closed at hyperpolarized membrane potentials. In response to membrane depolarization the channels open within a few hundred microseconds, resulting in an inward sodium flux, which is terminated within a few milliseconds by channel inactivation. In whole cell recordings, rapid activation and inactivation of thousands of sodium channels distributed throughout the cell membrane results in a transient inward sodium current that rises rapidly to peak amplitude and then decays to baseline within a few milliseconds. Among the channel properties that are likely to be altered by mutations linked to epilepsy are: 1) the voltage-dependence of activation, a measure of the strength of membrane depolarization

necessary to open the channels; 2) the voltage-dependence of steady state inactivation, a measure of the fraction of channels available to open at the resting membrane potential; and 3) the time course of inactivation. Preliminary results indicate that D188V mutant channels are identical to wild type channels with respect to the voltage-dependence of activation and to inactivation time course. However, steady state inactivation for the mutant channels is shifted to membrane potentials that are slightly more positive than observed in wild type channels. This positive shift should increase the fraction of channels available to open at rest. This could increase neuronal excitability and contribute to epileptogenesis. Thus, a functional consequence of a naturally occurring mutation in a sodium channel gene has been tentatively identified. Thus, the functional consequence of the D188M mutant could at least in part explain its role in epilepsy. Such a functional consequence is expected to be observed with other mutations identified above in SCNA1, SCNA2 and SCNA3.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

REFERENCES:

Andermann E (1982) Multifactorial inheritance of generalized and focal epilepsy. In: Anderson VE, Hauser WA, Penry JK, Sing CF (eds) Genetic Basis of the Epilepsies. New York, Raven Press, pp:355-374

Anderson MA and Gusella JF (1984) Use of cyclosporin A in establishing Epstein Barr virus-transformed human lymphoblastoid cell lines. In Vitro 20:856-858

Anneger JF, Hauser WA, Anderson VE (1982) Risk of seizures among relatives of patients with epilepsy: families in a defined population. In: Anderson VE, Hauser WA, Sing L, Porter R (eds) The Genetic Basis of the Epilepsies, Raven Press, New York, pp 151-159

Barnard EA, Darlison MG, Seeburg P (1987) Molecular biology of the GABAA receptor: the receptor/channel superfamily. Trends Neurosci 10:502-509.

Berkovic SF, et al. Epilepsies in twins: genetics of the major epileptic syndromes. Ann Neurol. 43:435-445 (1998).

Bievert C, Schoeder BC, Kubisch C, Berkovic SF, Propping P, Jentsch TJ, Steinlein OK (1998) A potassium channel mutation in neonatal human epilepsy. Science 279:403-406

Bu DF, Tobin AJ (1994) The exon-intron organization of the genes (GAD1 and GAD2) encoding two human glutamate decarboxylases (GAD67 and GAD65) suggests that they derive from a common ancestral GAD. Genomics 1:222-228.

Charlier C, et al. A pore mutation in a novel KGT-like potassium channel gene in an idiopathic epilepsy family. Nat. Genet. 18:53-55 (1998).

Commission on Classification and Terminology of the International League against Epilepsy (1989) Proposal for revised clinical and eletroencephalographic classification of epileptic seizures. Epilepsia 22:489-501

Corey LA, Berg K, Pellock JM, Solaas MH, Nance WE, DeLorenzo RJ (1991) The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. Neurology 41:433-436

Elmslie FV, Rees M, Williamson MP, Kerr M, Kjeldsen MJ, Pang KA, Sundqvist A, et al (1997) Genetic mapping of a major susceptibility locus for juvenile myoclonic epilepsy on chromosome 15q. Hum Mol Genet 6:1329-1334

Engel JJ, Pedley TA (1998) What is epilepsy ? In: Engel JJ, Pedley TA (eds) Epilepsy a Comprehensive Textbook, Lippincott-Raven Publishers, Philadelphia, pp:1-10.

Escayg et al., *Nature Genetics*. 24(4):343-5, 2000.

Greenberg DA, Delgado-Escueta AV, Widelitz H, Sparkes RS, Treiman L, Maldonado HM, et al (1988) Juvenile myoclonic epilepsy (JME) may be linked to the BF and HLA loci on human chromosome 6. Am J Hum Genet 31:185-192

Guipponi M, Rivier F, Vigevano F, Beck C, Crespel A, Echenne B, Lucchini P, et al (1997) Linkage mapping of benign familial infantile seizures (BFIS) to chromosome 19q. Hum Mol Genet 6:473-477

Gyapay G, Morissette J, Vignal A, et al. (1994) The 1993-94 Genethon human genetic linkage map. Nat Genet 7:246-339

Harvald B and Hauge M (1965) Hereditary factors elucidated by twin studies. In: Neel JV, Shaw MW, Schull WJ (eds) Genetics and the Epidemiology of Chronic Diseases, Washington Public Health Service Publications 1163:61-76

Inouye E (1960) Observations on forty twin index cases with chronic epilepsy and their co-twins. J Nerv Ment Dis 130: 401-416

Lathrop GM, Lalouel JM, (1984) Easy calculations of lod scores and genetic risks on small computers. Am J Hum Genet 36:460-465

Lennox WG, Lennox MA (1960) Epilepsy and related disorders. Boston, Little Brown.

Leppert M, Anderson VE, Quattlebaum T, Staufe D, O'Connell P, Nakamura Y, Lalouel JM, et al (1989) Benign familial neonatal convulsions linked to genetic markers on chromosome 20. Nature 337:647-648

Lewis TB, Leach RJ, Ward K, O'Connell P, Ryan SG (1993) Genetic Heterogeneity in benign familial neonatal convulsions: identification of a new locus on chromosome 8q. Am J Hum Genet 53:670-675

McPhee et al., 1998, J. Biol. Chem. 273:1121-1129

Ottman R, Annegers JF, Hauser WA, Kurland LT (1989) Seizure risk in offspring of parents with generalized versus partial epilepsy. Epilepsia 30:157-161

Ottman R, Hauser WA, Barker-Cummings C, Lee JH, Risch N (1997) Segregation analysis of cryptogenic epilepsy and an empirical test of the validity of the results. Am J Hum Genet 60:667-675

Sambrook J, Fritsch EF, Maniatis T (eds) (1989) Molecular cloning: a laboratory manual, 2nd ed. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pp E.3-E.4

Scheffer IE and Berkovic SF (1997) Generalised epilepsy with febrile seizures plus: a genetic disorder with heterogeneous clinical phenotypes. Brain 120: 479-490.

Schroeder et al.,1998, Nature 396:687-690.

Silanpaa M, Koskenvuo M, Romanov K, Kaprio J (1991) Genetic factors in epileptic seizures: evidence from a large twin population. Acta Neurol Scand 84:523-526

Singh NA, Charlier C, Stauffer D, DuPont BR, Leach RJ, Melis R, Ronen GM, et al (1998) A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. Nat Genet 18:25-29

Steinlein OK, et al. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. Nat. Genet. 11:201-203 (1995).

Wallace RH, Wang DW, Sing R, Scheffer IE, George-Jr AL, Phillips HA, Saar K, et al (1998) Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel (1 subunit gene SCN1B. Nat Genet 19:366-370

WHAT IS CLAIMED IS:

1. A method of determining an individual's predisposition to epilepsy and/or development of epilepsy, as well as predicting this individual's response to medication, said method comprising the step of determining the genotype of at least one gene selected from SCN1A, SCN2A and SCN3A of the individual, or of a DNA variant, equivalent, or mutation which shows a linkage disequilibrium therewith, thereby determining an individual's predisposition to epilepsy and/or development of epilepsy.

2. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises restriction endonuclease digestion.

3. The method of claim 1 or 2, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises hybridizing with allele specific oligonucleotides.

4. The method of claim 1, which further comprises a step, prior to determining the SCN1A, SCN2A or SCN3A genotype, of amplifying a segment of the the SCN1A, SCN2A or SCN3A using polymerase chain reaction.

5. The method of claim 1, wherein the step of determining the SCN1A, SCN2A or SCN3A genotype comprises a sequencing of SCN1A, SCN2A or SCN3A , or parts thereof.

6. The method of claim 1, wherein the SCN1A, SCN2A or SCN3A genotype is determined using a polymorphic variant

site in linkage disequilibrium with at least one allelic variant or mutant identified in accordance with the present invention.

7. An assay for screening a test agent and selecting an agent which modulates inactivation of a sodium channel involved in epilepsy comprising:

a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and

b) assaying a function of said sodium channel;

wherein an agent can be selected when an observable difference is observed between the inactivation of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

8. An assay for screening a test agent and selecting an agent which modulates the activity of a sodium channel involved in epilepsy comprising:

a) a recombinant SCN1A, SCN2A or SCN3A gene which encodes an alpha subunit of said sodium channel or functional fragment thereof; and

b) assaying the activity of said sodium channel;

wherein an agent can be selected when an observable difference is observed between the activity of said sodium channel in the presence of said test agent, as compared to in an absence thereof, and wherein a malfunction of said sodium channel is associated with epilepsy.

9. A method of using specific alleles of the SCN1A, SCN2A or SCN3A genes, or a variant, equivalent, or mutation thereof which shows linkage disequilibrium therewith, to set-up a screening assay

for agents destined to modulate sodium channel function for the purpose of identifying agents having an application in epilepsy therapy.

10. A method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising:

a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;

b) contacting said screening assay with a test compound; and

c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

11. The method of claim 10, wherein the test compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide further analogs of said test compound also having said therapeutic effect.

12. A compound having therapeutic effect on epilepsy or other neurological disorders, identified by a method comprising,

a) providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene;

b) contacting said screening assay with a test compound; and

c) detecting if said test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene;

wherein a test compound which modulates said biological activity is a compound with said therapeutic effect.

13. The compound of claim 12, wherein the compound with said therapeutic effect is further modified by combinatorial or medicinal chemistry to provide analogs of said compound also having said therapeutic effect.

Ch 2q23-q31

Centromere

1cM

D2S142

D2S284

4cM

D2S156/

4cM

D2S354

D2S111

5cM

D2S294

2cM

D2S335

IGE locus

6cM

29 cM

D2S324

2cM

D2S384

2cM

D2S152

8cM

Telomere

D2S311

Fig. 1

1Ax00.1
NaC-340 TGTGTTCTGCCCCAGTGAGACT,
NaC-341 CTTCCTGCTCTGCCCAAACTGAAT
257 bp 53.4C

1Ax00.2
NaC-342 GGCGATGTAATGTAAGGTGCTGTC,
NaC-343 GTGCCTTCAGTTGCAATTGTTCAG
259 bp 54.5C

1Ax01.1
NaC-268, TTAGGAATTTCATATGCAGAATAA,
NaC-269 TGGGCCATTTTTCGTCGTC
201 bp 50.9C

1Ax01.2
NaC-270 GAAAGACGCATTGCAGAAGAAAAGG,
NaC-271 CTATTGGCATGTGTTGGTGCTACA
277 bp 54.4C

1Ax02
NaC-45 GTGCTGGTTTCTCATTTAACTTTAC,
NaC-46 TTCCCAACTTAATTTGATATTTAGC
319 bp 49.9C

1Ax03
NaC-87, GCAGTTTGGGCTTTTCAATGTTAG,
NaC-88, GACACAGTTTCARAATCCCRAATG
234 bp 48.9C

1Ax04
NaC-63, TTAGGGCTACGTTTCATTTGTATG,
NaC-64, AGCACTGATGGAAAACCAAACTAT
338 bp 50.8C

1Ax05
NaC-164 AGCCCATGCAGTAATATAAATCCT,
NaC-165 TCCAGGCTGATAAGCTATGTCTAA
488 bp 52.8C

FIG 2

1Ax06
NaC-276, CTGTGGCCTGCCTGAGCGTATT,
NaC-277 CCAATTCTACTTTTTAAGGAAATG
248 bp 50.3C

1Ax07
NaC-272, AAATACTTGTGCCTTTGAA,
NaC-273, GTACATACAATATACACAGATGC
240 bp 46.7C

1Ax08
Nac-89, AGGCAGCAGAACGACTTGTAATA,
NaC-90, ATCCGGTTTTAATTTCATAACTCA
267 bp 51.9C

1Ax09.2
NaC-217 GTTGAGCACCCTTAGTGAATAATA,
NaC-218 TCACACGCTCTAGACTACTTCTCT
337 bp 52.7C

1Ax10a NaC-29, TGCAAATACTTCAGCCCTTTCAAA,
NaC-30, TTCCCCACCAGACTGCTCTTTC
239 bp 55.1C

1Ax10a
NaC-31, GCAGCAGGCAGGCTCTCA,
NaC-32, TCTCCCATGTTTTAATTTTCAACC
293 bp 54.5C

1Ax10b
NaC-67, ATAATCTTGCAAAATGAAATCACA,
NaC-68, ATCCGGGATGACCTACTGG
307 bp 53.7C

1Ax10b
NaC-65, GATAACGAGAGCCGTAGAGATTCC,
NaC-66, AGCCAGCCATGCCTGAACTA
282 bp 56.4C

Fig 2 (cont'd)

1Ax10c
NaC-39, TGTTTGCTTGTCATATTGCTCAA,
NaC-40, TGCACTATTCCCAACTCACAAA
286 bp 50.7C

1Ax11.1
NaC-69 AAGGGTGTCTCTGTAACAAAAATG,
NaC-70, GTGATGGCCAGGTCAACAAA
269 bp 50.8C

1Ax11.2
NaC-71 CTGGGACTGTTCTCCATATTGGTT,
NaC-72, TTTGCAGGGGCCAGGAAG
294 bp 53.3°C

1Ax12
NaC-41 CATTGTGGGAAAATAGCATAAGC,
NaC-42, GCAAGAACCCTGAATGTTAGAAA
334 bp 51.2C

1Ax13.1
NaC-92 TAATGCTTTTAAGAATCATACAAA,
NaC-93, CCAGCGTGGGAGTTGACAATC
256 bp 51.1C

1Ax13.2
NaC-75 CGGCATGCAGCTCTTTGGTA,
NaC-91, ATGTGCCATGCTGGTGTATTTC
277 bp 55.6C

1Ax14.1
NaC-79 CACCCATCTTCTAATCACTATGC,
NaC-80, CAGCAATTTGGAGATTATTCATT
254 bp 50.4C

1Ax14.2
NaC-81 GCAGCCACTGATGATGATAA,
NaC-82, CTGCCAGTTCCTATACCACTT
269 bp 49.4C

Fig - 2 (cont'd)

1Ax14.3
NaC-83 TACAGCAGAAATTGGGAAAGAT,
NaC-84, GTATTCATACCTACCCACACCTAT
269 bp 50.2C

1Ax15
NaC-202 TTCTTGGCAGGCAACTTATTACC,
NaC-203 TAAGCTGCACTCCAAATGAAAGAT
233 bp 53.1C

1Ax16.1
NaC-187, GGCTGAATGTTTCCACAACT,
NaC-168 GTTCAACTATTCGGAAACACG
277 bp 51.4C

1Ax16.2
NaC-188, AGGCAGAGGAAAACAATGG,
NaC-189, ACAAGGTGGGATAATTAAAAATG
234 bp 50.3C

1Ax17
NaC-143, GTTTCTCTGCCCTCCTATTCC,
NaC-144, AAGCTACCTTGAACAGAGACA
330 bp 48.8C

1Ax18
NaC-139, AATGATGATTCTGTTTATTA,
NaC-140, AATTTGCCATTCCTTTTG
272 bp 46.1C

1Ax19.1
NaC-219 TTGACATCGAAGACGTGAATAATC,
NaC-220 CCATCTGGGCTCATAAACTTGTA
285 bp 49.3C

1Ax20
NaC-338 CCCTTTGAAAATTATATCAGTAA,
NaC-339 ATTTGGTCGTTTATGCTTTATTC
230 bp 47.6C

FIG 2 (cont'd)

1Ax21
NaC-252, TCCAGCACTAAAATGTATGGTAAT,
NaC-253, ATTTGGCAGAGAAAACACTCC
261 bp 49.8C

1Ax22
NaC-254, TTTTAGCCATCCATTTTCTATTTT,
NaC-255, TATTTTCCCCCATATCATTTGA
223 bp 49.1C

1Ax23.1
NaC-256 TTTGCAAGAAACTAGAAAGTC,
NaC-257 TTGATGCGTGACAAAATGG
250 bp 48.3C

1Ax23.2
NaC-258 GACCAGAGTGAATATGTGACTACC,
NaC-259 CTGGGATGATCTTGAATCTAATC
246 bp 49.5C

1Ax24.1
NaC-221 GCAACTCAGTTCATGGAATTTGAA,
NaC-222 CTTGTTTTCGTTTTAAAGTAGTA
289 bp 56.1C

1Ax24.2
NaC-213 CAAAGATCACCCTGGAAGCTCAGTT,
NaC-223 TTCAAGCGCAGCTGCAAACTGAGAT
277 bp 55.8C

1Ax24.3
NaC-260 ACATCGGCCTCCTACTCTTCCTA,
NaC-261 ACAGATGGGTTCCCACAGTCC
268 bp 55.3C

1Ax24.4
NaC-262 TAACGCATGATTTCTTCACTGGTT,
NaC-263 ATCCCAAAGATGGCGTAGATGA
262 bp 54.9C

Fig 2 (cont'd)

1Ax24.5
NaC-308, TGAGAAATAGGCTAAGGACCTCTA,
NaC-309 CCTAGGGGCTGGATTCC
244 bp 53.2C

1Ax24.6
NaC-310, AAGGGGTGCAAACCTGTGATTTT,
NaC-311 AGGGCCATGTGGTTGCCATAC
252 bp 53.4C

1Ax24.7
NaC-312 CTTCCGGTTTATGTTTTCATTTCT,
NaC-313 TCTTTATTAGTTTTGCACATTTTA
278 bp 48.4C

1Ax24.8
NaC-364 CAATCCTTCCAAGGTCTCCTATC,
NaC-365 TTTCATCTTTGCCTTCTTGCTCAT
326 bp 52.4C

1Ax24.9
NaC-366 CATGTCCACTGCAGCTTGTCCA,
NaC-367 TCCCCTTTACACAGAGTCACAGTT
292 bp 53.1C

FIG - 2 (cont'd)

a. Glu1238Asp:

normal: GCA TTT GAA GAT ATA;

patient R10191 with IGE: GCA TTT GAC GAT ATA.

b. Ser1773Tyr:

normal: ATC ATA TcC TTC CTG;

patient R9049 with IGE: ATC ATA TmC TTC CTG; TCC>TAC

Fig 3

2Ax00.1 NaC-235 ATGGGTTGAATGACTTTCTGACAT, NaC-236, AGGCATTTCCTGTACAGGGACTAC
266 bp 52.7C

2Ax00.2 NaC-237 ACAGGAAATGCCTCTTCTTACTTC, NaC-238, TTTCCCCAAGGATTCTACTACTGT
277 bp 50.6C

2Ax01 NaC-100, AGTGCATGTAACTGACACAATCAC, NaC-101, CTTGCGTTCCTGTTTGGGTCTCT
241 bp 53.7C

2Ax01 NaC-11 TCCGCTTCTTTACCAGGGAATC, NaC-102, AGGCAGTGAAGGCAACTTGACTAA
259 bp 55.1C

2Ax02 NaC-96, CAGGGCAATATTTATAAATAATGG, NaC-97, TTTGGAAAATGTGTAGCTCAATAA
289 bp 48.7C

2Ax03 NaC-43, AAGGCATGGTAGTGCATAAAAG, NaC-44, ATGAAACATAAAGGGAGGTCAA
201 bp 49.3°C

2Ax04 NaC-47, AATGTGAGCTTGGCTATTGTCTCT, NaC-48, ATAGGCTCCCACCAGTGATTTAC
213 bp 50.9°C

2Ax05 NaC-49, AGGCCCCTTATATCTCCAACTG, NaC-50, CAACAAGGCTTCTGCACAAAAG
241 bp 53.9°C

2Ax05.2 NaC-110, CTTGGTGGCTTGCCTTGAC, NaC-111, TCATGAGTGTCGCCATCAGC
223 bp 51.1C

Fig 4

2Ax05.3 NaC-112, GGAAAGCTGATGGCGACACT, NaC-113, CTGAGACATTGCCCAGGTCC
329 bp 53.0C

2Ax05.4 NaC-114, TTTTTACCCGTTGCTTTCTTTA, NaC-115, TATCCCTTGCTCTTTCATTTATCT
224 bp 50.9C

2Ax06.1 NaC-169, GCCGGTAAAATAGCTGTTGAGTAG, NaC-170, GCCATTGCAAACATTTATTTCGTA
206 bp 53.3C

2Ax06.2 NaC-171, GCGTGTTTGCGCTAATAG, NaC-172, CTAAGTCACTTGATTCACATCTAA
295 bp 48.0C

2Ax07 Nac-196, ACAGGGTGGCTGAAGTGTTTTA, NaC-197, GTGGGAGGTGGCAGGTTATT
199 bp 52.6C

2Ax08 NaC-118, CAATTAGCAGACTTGCCGTTATT, NaC-119, TCTCTTGAGTTCGGTGTTTTATGA
252 bp 52.9C

2Ax09 NaC-120, ACCGAACTCAAGAGAATTGCTGTA, NaC-121, AAAGGACCGTATGCTTGTTCACTA
334 bp 52.9C

2Ax10a.1 NaC-161 TATGAATGCGCATTTTACTCTTTG, NaC-156, TGGAGCTCAACTTAGATGCTACTG
286 bp 52.1C

2Ax10a.2 NaC-13 GGTGCTGGTGGGATAGGAGTTTTT, NaC-162, TCCATTAAATTCTGGCATATTCTT
316 bp 50.9C

2Ax10b.1 NaC-145 TCAGAGGGGTGCTTTCTTCCACAT, NaC-14, CTTCGGCTGTCATTGTCCTCAAAG
298 bp 55.6C

Fig 4 (cont'd)

2Ax10b.2 NaC-146,GCAAAGGACATTGGCTCTGAGAAT, NaC-147, CTGCCTGCACCAGTCACAACTCT
324 bp 59.4C

2Ax10c NaC-190, TGGGCTTTGCTGCTTTCAA, NaC-191, AGTAACTGTGACGCAGGACTTTTA
218 bp 51.5C

2Ax11.1 NaC-148, CCCTGTTCCTCCAGCAGATTA, NaC-70, GTGATGGCCAGGTCAACAAA
283 bp 51.5C

2Ax11.2 NaC-149,TTTGATTTGGGACTGTTGTAAAC, NaC-150, AAGGCAATTATAAACTCTTTCAAG
233 bp 52.0C

2Ax12 NaC-159, TGGGAGTTAAATTAAGTTGCTCAA, NaC-160, ACATTTTATGAACACTCCCAGTTA
285 bp 50.4C

2Ax13.1 NaC-239 ATTAACACTGTTCTTGCTTTTAT, NaC-240, GTGCCAGCGTGGGAGTTC
239 bp 51.1C

2Ax13.2 NaC-241 GTGGGGGCTCTAGGAAACCT, NaC-242, TTTAATGAAAATGAGGAAAATGTT
324 bp 53.7C

2Ax14.1 NaC-134, GACCAAGCATTTTTATTTCATTC, NaC-135, AGTGGCAGCAAGATTGTCA
234 bp 49.6C

2Ax14.2 NaC-136, GGCCTTGCTTTTGAGTTCC, NaC-137, GGTCTTTGCCTATTTCTATGGTG
257 bp 51.1C

Fig 4 (cont'd)

2Ax14.3 NaC-266, TTAAACCGCTTGAAGATCTAAATA, NaC-267,
TATACACCAAAATATCTCCTTAT
319 bp 48.5C

2Ax15 NaC-314 GGGGCACACCTAATTAATTTTTAT, NaC-315,
AAAGAGGATACTCAAGACCACATA
(247 bp) 51.5C

2Ax16 NaC-344 CCCACCAACACAAATATACCTAAT, NaC-345,
TGAAGGGAAAGGGAAAAGATTT
283 bp 52.2C

2Ax17 NaC-346 TCCAGCCTTAGGCACCTGATAA, NaC-347,
ATAAAGCAGCAAAGTGCAGCATAC
310 bp 52.4C

2Ax18 NaC-348 AAGGCTGAACTGTGTAGACATTTT, NaC-349,
TGACATTTCCATGGTACAAAGTGT
262 bp 52.2C

2Ax19.1 NaC-350 TTTGTTGTTGGCTTTTCACTTAT, NaC-351,
CCACCTGGCAGTTTGATTG
268 bp 51.9C

2Ax19.2 NaC-352 TAAGCGTGGTCAACAACTACAGT, NaC-353,
ATTCTTGCCAGCATTTATTGTC
260 bp 50.2C

2Ax20 NaC-354 CAAAACATTGCCCCAAAAG, NaC-355,
TCAAACTAAACAATTTCCCTCTAA
239 bp 48.1C

2Ax21 NaC-306, GATAATTAAAAACTCACTGATGTA, NaC-307,
GGAGGCTAAAGGAAAGAGTATG
288 bp 46.6C

2Ax22 NaC-356 ATTTTATAGCCAGCAAAGAACAC, NaC-357,
CTAGAAATTCGGGCTGTGAA
230 bp 49.6C

Fig 4 (cont'd)

2Ax23.1 NaC-358 CTGCTTTGTGACCTAAGGCAAGTT, NaC-359, GTGACCATGTTAAGGCAGATGAGG
290 bp 51.4C

2Ax23.2 NaC-360 GGAATGGTCTTTGATTTTGTAACC, NaC-361, TCCTTAACTGAATAAAAGCACCTC
290 bp 51.6C

2Ax24.1 NaC-207 TGGAACACCCATCAAAGAAGATACT, NaC-208, GTGGGAGTCCTGTTGACACAAAC
278 bp 52.8C

2Ax24.2 NaC-209 AGCGATTCATGGCATCAAAC, NaC-210, ACGTGGTGGAAGGCGTCATA
270 bp 52.9C

2Ax24.3 NaC-211 GCGACCCAGTTTATAGAGTTTGCC, NaC-212, CTTGTTTGCGTTTCAACGTGGTC
289 bp 56.1C

2Ax24.4 NaC-213 CAAAGATCACCCTGGAAGCTCAGTT, NaC-214, ATCCAGGGCATCTGCAAAATCAGAA
277 bp 55.8C

2Ax24.5 NaC-215 TGCCTATGTTAAGAGGGAAGTTGGG, NaC-216, ATGACCGCGATGTACATGTTCAG
279 bp 55.3C

2Ax24.6 NaC-278 TCAATTGTTTACAGCCCGTGATG, NaC-279, TTTATACAAAGGCAGACAACAT
302 bp 52.0C

2Ax24.7 NaC-280 AGGCGTAATGGCTACTCAGACGA, NaC-281, GTAATCCCTCTCCCCGAACATAAAC
251 bp 53.8C

2Ax24.8 NaC-282 TTTGATTCACGGGTTGTTTACTCTTA, NaC-283, TTCTATGGAACATTTACAGGCACATT
294 bp 52.1C

Fig 4 (cont'd)

2Ax24.9 NaC-284 TAATGTGCCTGTAAATGTTCCATAGA, NaC-285, CAGGCTTCTTAGAAAGGACTGATAGG
264 bp 50.6C

2Ax24.10 NaC-286 GTCCCAGCAGCATGACTATC, NaC-287, CCCACTGGGTAAAATTACTAAC
249 bp 49.4C

2Ax24.11 NaC-288 TAGCCATCTTCTGCTCTTGGT, NaC-289, TGGCTTCCCATATTAGACTTCTG
307 bp 51.3C

2Ax24.12 NaC-290 TCTTGCCTATGCTGCTGTATCTTA, NaC-291, AGTCGGGCTTTTCATCATTGAG
207 bp 51.8C

2Ax24.13 NaC-292 TTCTTCATGTCATTAAGCAATAGG, NaC-293, TTCAATTTAAAAGTGCTAGGAACA
299 bp 49.4C

2Ax24.14 NaC-294 CTTCAGGTGGATGTCACAGTCACTA, NaC-295, ATTCAAGCAATGCCAAGAGTATCA
263 bp 51.5C

2Ax24.15 NaC-296 CTTTCAATAGTAATGCCTTATCAT, NaC-297, TCCTGCATGCATTTCACCAAC
348 bp 49.6C

2Ax24.16 NaC-362 CTGTTCACATTTTGTAAAACTAAT, NaC-263, ATCCCAAAGATGGCGTAGATGA
309 bp 50.8C

2Ax24.17 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-363, GATCTTTGTCAGGGTCACAGTCT
269 bp 54.0C

Fig 4 (cont'd)

a. Lys908Arg:
normal: TAC AAA GAA;
9782 (Patient with IGE): TAC AGA GAA;

b. leu768val, in individuals 8197, 9062 et 9822 (all IGE patients).

FIG - 5

3Ax00a.1 NaC-390 TGTGTCCGCCAGTAGATGG, NaC-391,
TTTTTGACCACAGAGGTTTACAA
233 bp 51.4C

3Ax00a.2 NaC-392 GAAGCGGAGGCATAAGCAGA, NaC-393,
GGTGCAGATAATGAAATGTTTTGT
253 bp 51.3C

3Ax00b NaC-394 CACCCCTATGCCAAATGTCAAAGA, NaC-395,
CAAAAACAAACTTATACCCAGAAG
293 bp 51.6C

3Ax00c NaC-396 CAAATATTGGGCAAACCCTAAT, NaC-397,
AAGGTGCCATCACAAAATCAT
225 bp 50.7C

3Ax01.1 NaC-51 ATCGCTTGCTTTCCTAACTCTTGT, NaC-52,
AAGTCACTATTTGGCTTTGGTTG
260 bp 53.1C

3Ax01.2 NaC-53 AGAAGCCCAAAAAGGAACAAGATA, NaC-54,
GGCCCAGAAAAGTATATTACAGTT
231 bp 50.8C

3Ax02 NaC-85, TCCTTAAATAAGCCCATGTCTAAT, NaC-86,
TCTCAAAGAAATTTTACAGATACT
273 bp 47.3C

3Ax03 NaC-27, AATGGCCATGGTAACCTACTAACA, NaC-28,
CAGGCTATACCCACAAGGAGATT
212 bp 51.8C

3Ax04 NaC-94, TGTTAATTTTGGCTTGGATGTT, NaC-95,
TCACTCCTTTGCGCTTATCAA
198 bp 50.8C

3Ax05.1 NaC-247, AGGGCTCTATGTGCCAAACC, NaC-248,
AGGGGCCTACTACCTTACACCAG
213 bp 52.2C

FIG - 6

3Ax05.2 NaC-249 TGTAATCCCAGGTAAGAAGAAAC, NaC-250,
TACCGGGATGAACTGTAATAATAA
304 bp 51.8C

3Ax06.1 NaC-192,TTCTGGCACTCTTCCTCAGGTAAC, NaC-193,
GTCCCATTTGAATCCATTGTGC
261 bp 55.4C

3Ax06.2 NaC-194,GGCCCCCAAGCGATTCTG, NaC-195,
TGTACACCCACAGTCTCAACTATT
209 bp 50.3C

3Ax07 NaC-204, ACAGCCACCTTTGTAAATAA, NaC-205,
TTTTTCGCAAAGAGTTCTAT
220 bp 46.6C

3Ax08 NaC-98, AAACTGACCCTACCTCCATTTCTC, NaC-99,
ACTCAGCCTATGCTTTTCATTTCA
247 bp 53.2C

3Ax09 NaC-37 CAGATATTTATTTGGGGACATTAT, NaC-38,
AAATCTTTGCKTTTATCACTCAGT
295 bp 52.0C

3Ax10a.1 NaC-198 TAGTGCCTGGCTTTGTTTTATGAC, NaC-199,
CGGATTTGGGAAAGCTGTCTCT
225 bp 54.3C

3Ax10a.2 NaC-200 AGAGCACCTTGAAGGAAACAACAA, NaC-274,
TCCCTCAACTGAAGTACAGATAGT
253 bp 51.2C

3Ax10b NaC-33, ATAATTGCGTTCTTCCCCTACCC, NaC-34,
AAGCCCTGGCACCATCCTG
301 bp 56.2°C

3Ax10c NaC-35, _TTTGCAAAGAAATGCTATGT, NaC-36,
CTGGGTAACAGACTTCAGTAAT
303 bp 51.4°C

Fig 6 (cont'd)

3Ax11.1 NaC-122, ATGGGATTGTCTTCTCAAGTTTCT, NaC-123, GATGGCAAGATCAACAAATGGA
294 bp 50.3C

3Ax11.2 NaC-124, CTTGATCTGGGACTGCTGTGATG, NaC-125, AGGATATAATTTTTGGTTCAACA
284 bp 51.5C

3Ax12 NaC-61, TTTTCAGTGCTCTTGATAGTAGTG, NaC-62, GTGCCAATGAGCGACAGG
254 bp 50.7°C

3Ax13.1 NaC-73, CCACGTGTGGTTCTATGATACC, NaC-74, ACCGTGGGAGCGTACAGTCA
298 bp 52.3C

3Ax13.2 NaC-75, CGGCATGCAGCTCTTTGGTA, NaC-76, TGGCCACGTTCCTAGCTACTGTC
291 bp 55.9C

3Ax14.1 NaC-55, GAGTTCCCTTTTTAGGCTGTTATT, NaC-56, TCTTATTGCCTTCATGGATTTCTA
285 bp 50.5C

3Ax14.2 NaC-57, TGAAAAATAAGATGCGGGAGTG, NaC-58, GTGAGGCTGGGGTTGTTTATG
247 bp 51.7C

3Ax14.3 NaC-59, GAGATGGGAATGGAACCACCA, NaC-60, TTCGATAATGCATATAAGCACAA
297 bp 51.7C

3Ax15 NaC-318 AAGGGGGAAAATCACATCTTT, NaC-319, TTAAATGAGGCATATTCAGTCTCC
235 bp 51.8C

3Ax16 NaC-116, GGAAGTGGAGTGGGGAAGG, NaC-117, ATTCTTGCCAATATGCATTTCACT
271 bp 51.1C

FIG 6 (cont'd)

3Ax17 NaC-157,TTCTTTTGTACTCACTATTATACTAA, NaC-158,
AAACTTGCCTCTTTTAAAAACAAT
317 bp 46.6C

3Ax18 NaC-374 TACCACACCCTATACCTTCAGTCA, NaC-375,
GAGTATGGCACCCTTTTCTATCTA
275 bp 51.4C

3Ax19.1 NaC-386 GCTATGTTCCCCTCGCTGTCT, NaC-387,
TGCTTGCCAAGAGCCTGAC
231 bp 53.6C

3Ax19.2 NaC-388 GCTGGCAAGTTCTACCACTGTG, NaC-389,
CAAACGAAGAACATCAGGGAAATA
247 bp 53.0C

3Ax20 NaC-376 TTCACAATATTGTACAAAAAGTTA, NaC-377,
ATTACCACCAATATTCACCATAAG
230 bp 46.4C

3Ax21 NaC-378 TCAGGGTAAGGCAAAAGTAGCAC, NaC-379,
GAACCCCAGAATGAAGAAAGGTAA
294 bp 50.2C

3Ax22 NaC-380 TTTGTGAAAGTACTATTGGAACAC, NaC-381,
ACGCATGGCTTTGGAACAT
204 bp 49.6C

3Ax23.1 NaC-382 CCCGTATGTGGAAGGGCTTTAT, NaC-383,
CTAGGTTGATCCGGGACAAAACTA
246 bp 52.9C

3Ax23.2 NaC-384 AACGGATGACCAGGGCAAATAC, NaC-385,
CTAGAAGGTCCTGGGGCAACTG
234 bp 54.8C

3Ax24.1 NaC-317 AAGCCATCATGTAAAGTGAAAAG, NaC-320,
ATCCCAAAGATGGCATAGATA
274 bp 52.5C

Fig 6 (cont'd)

3Ax24.2 NaC-325 CACGCTGCTCTTTGCTTTGA, NaC-326, TGAGCTGCCAGGGTGAATTG
282 bp 54.9C

3Ax24.3 NaC-327 TTGCTAGCACCTATTCTTAATAGTGC NaC-328, CCAGGGCAGCTGCAAAATCAGAG
318 bp 54.2C

3Ax24.4 NaC-329 CCCGATGCGACCCAGTTTA, NaC-330, TGGAGGGGTTTGATGCCATA
250 bp 55.2C

3Ax24.5 NaC-331 GATGGATGCCCTTCGAATACAGA, NaC-332, TTCCCATTTAGTTTGTCAATAATC
258 bp 50.6C

3Ax24.6 NaC-321 AAGGGGAGGATTGACTTACCTAT, NaC-333, TTGGCATGGACCTCCTCTTGA
302 bp 51.5C

Fig 6 (cont'd)

a. Asn43DEL:
9706 (allele 1; IGE patient): CAA GAT AAT GAT GAT GAG ;
9632 (allele 2; patient has IGE): CAA GAT --- GAT GAT GAG ;
allele 1 = 131/146 (0.90);
allele 2= 15/146 (0.10);
for IGE patients: homozygotes (22): 3958, 9632; heterozygotes (12): 9049, 9152, 9649, 9710, 9896, 10069, 10191, 10213, 9993, 10009, 10256 (note that 2 patients are homozygous for the rare allele; all patients have IGE); in controls: allele 1 = 45/154 (0.94); allele 2 = 9/154 (0.06) and no 22 homozygotes found.

b. normal: tggtgtaaggtag,
10670 (IGE patient): tggtataaggtag

c. normal: ccccttatatctccaac,
10250 (IGE patient): ccccttatayctccaac;

d. Val1035Ile:
normal: AAA TAC GTA ATC GAT,
9269 (IGE patient): AAA TAC RTA ATC GAT; GTA>ATA = Val>Ile.

Fig - 7

SEQUENCE LISTING

<110> McGill University
Rouleau, Guy A.
Lafrenière, Ronald G.
Cossette, Patrick
Ragsdale, David

<120> LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSE OR OR TREAT EPILEPSY

<130> 13180.17

<140> PCT/CA00/01404
<141> 2000-11-24

<160> 408

<170> PatentIn Ver. 2.1

<210> 1
<211> 8378
<212> DNA
<213> Homo sapiens

<400> 1
tactgcagag gtctctggtg catgtgtgta tgtgtgcgtt tgtgtgtgtt tgtgtgtctg 60
tgtgttctgc cccagtgaga ctgcagccct tgtaaatact ttgacacctt ttgcaagaag 120
gaatctgaac aattgcaact gaaggcacat tgttatcatc tcgtctttgg gtgatgctgt 180
tcctcactgc agatggataa ttttcctttt aatcaggaat ttcatatgca gaataaatgg 240
taattaaaat gtgcaggatg acaagatgga gcaaacagtg cttgtaccac caggacctga 300
cagcttcaac ttcttcacca gagaatctct tgcggctatt gaaagacgca ttgcagaaga 360
aaaggcaaag aatcccaaac cagacaaaaa agatgacgac gaaaatggcc caaagccaaa 420
tagtgacttg gaagctggaa agaaccttcc atttatttat ggagacattc ctccagagat 480
ggtgtcagag cccctggagg acctggaccc ctactatatc aataagaaaa cttttatagt 540
attgaataaa gggaaggcca tcttccggtt cagtgccacc tctgccctgt acattttaac 600
tcccttcaat cctcttagga aaatagctat taagattttg gtacattcat tattcagcat 660
gctaattatg tgcactattt tgacaaactg tgtgtttatg acaatgagta accctcctga 720
ttggacaaag aatgtagaat acaccttcac aggaatatat acttttgaat cacttataaa 780
aattattgca aggggattct gtttagaaga ttttactttc cttcgggatc catggaactg 840
gctcgatttc actgtcatta catttgcgta cgtcacagag tttgtggacc tgggcaatgt 900
ctcggcattg agaacattca gagttctccg agcattgaag acgatttcag tcattccagg 960
cctgaaaacc attgtgggag ccctgatcca gtctgtgaag aagctctcag atgtaatgat 1020
cctgactgtg ttctgtctga gcgtatttgc tctaattggg ctgcagctgt tcatgggcaa 1080
cctgaggaat aaatgtatac aatggcctcc caccaatgct tccttggagg aacatagtat 1140
agaaaagaat ataactgtga attataatgg tacacttata aatgaaactg tctttgagtt 1200
tgactggaag tcatatattc aagattcaag atatcattat ttcctggagg gtttttttaga 1260

tgcactacta tgtggaaata gctctgatgc aggccaatgt ccagagggat atatgtgtgt 1320
gaaagctggt agaaatccca attatggcta cacaagcttt gataccttca gttgggcttt 1380
tttgtccttg tttcgactaa tgactcagga cttctgggaa aatctttatc aactgacatt 1440
acgtgctgct gggaaaacgt acatgatatt ttttgtattg gtcattttct tgggctcatt 1500
ctacctaata aatttgatcc tggctgtggt ggccatggcc tacgaggaac agaatcaggc 1560
caccttggaa gaagcagaac agaaagaggc cgaatttcag cagatgattg aacagcttaa 1620
aaagcaacag gaggcagctc agcaggcagc aacggcaact gcctcagaac attccagaga 1680
gcccagtgca gcaggcaggc tctcagacag ctcatctgaa gcctctaagt tgagttccaa 1740
gagtgctaag gaaagaagaa atcggaggaa gaaaagaaaa cagaaagagc agtctggtgg 1800
ggaagagaaa gatgaggatg aattccaaaa atctgaatct gaggacagca tcaggaggaa 1860
aggttttcgc ttctccattg aagggaaccg attgacatat gaaaagaggt actcctcccc 1920
acaccagtct ttgttgagca tccgtggctc cctattttca ccaaggcgaa atagcagaac 1980
aagccttttc agctttagag ggcgagcaaa ggatgtggga tctgagaacg acttcgcaga 2040
tgatgagcac agcacctttg aggataacga gagccgtaga gattccttgt ttgtgccccg 2100
acgacacgga gagagacgca acagcaacct gagtcagacc agtaggtcat cccggatgct 2160
ggcagtgttt ccagcgaatg ggaagatgca cagcactgtg gattgcaatg gtgtggtttc 2220
cttggttggt ggaccttcag ttcctacatc gcctgttgga cagcttctgc cagaggtgat 2280
aatagataag ccagctactg atgacaatgg aacaaccact gaaactgaaa tgagaaagag 2340
aaggtcaagt tctttccacg tttccatgga ctttctagaa gatccttccc aaaggcaacg 2400
agcaatgagt atagccagca ttctaacaaa tacagtagaa gaacttgaag aatccaggca 2460
gaaatgccca ccctgttggt ataaattttc caacatattc ttaatctggg actgttctcc 2520
atattggtta aaagtgaaac atgttgtcaa cctggttgtg atggacccat ttgttgacct 2580
ggccatcacc atctgtattg tcttaaatac tcttttcatg gccatggagc actatccaat 2640
gacggaccat ttcaataatg tgcttacagt aggaaacttg gttttcactg ggatctttac 2700
agcagaaatg tttctgaaaa ttattgccat ggatccttac tattatttcc aagaaggctg 2760
gaatatcttt gacggtttta ttgtgacgct tagcctggta gaacttggac tcgccaatgt 2820
ggaaggatta tctgttctcc gttcatttcg attgctgcga gttttcaagt tggcaaaatc 2880
ttggccaacg ttaaatatgc taataaagat catcggcaat tccgtggggg ctctgggaaa 2940
tttaaccctc gtcttggcca tcatcgtctt cattttgcc gtggtcggca tgcagctctt 3000
tggtaaaagc tacaaagatt gtgtctgcaa gatcgccagt gattgtcaac tcccacgctg 3060
gcacatgaat gacttcttcc actccttcct gattgtgttc cgcgtgctgt gtggggagtg 3120
gatagagacc atgtgggact gtatggaggt tgctggtcaa gccatgtgcc ttactgtctt 3180
catgatggtc atggtgattg gaaacctagt ggtcctgaat ctctttctgg ccttgcttct 3240
gagctcattt agtgcagaca accttgcagc cactgatgat gataatgaaa tgaataatct 3300
ccaaattgct gtggatagga tgcacaaagg agtagcttat gtgaaaagaa aaatatatga 3360
atttattcaa cagtccttca ttaggaaaca aaagatttta gatgaaatta aaccacttga 3420
tgatctaaac aacaagaaag acagttgtat gtccaatcat acagcagaaa ttgggaaaga 3480
tcttgactat cttaaagatg taaatggaac tacaagtggt ataggaactg gcagcagtgt 3540
tgaaaaatac attattgatg aaagtgatta catgtcattc ataaacaacc ccagtcttac 3600
tgtgactgta ccaattgctg taggagaatc tgactttgaa aatttaaaca cggaagactt 3660
tagtagtgaa tcggatctgg aagaaagcaa agagaaactg aatgaaagca gtagctcatc 3720
agaaggtagc actgtggaca tcggcgcacc tgtagaagaa cagcccgtag tggaacctga 3780
agaaactctt gaaccagaag cttgtttcac tgaaggctgt gtacaaagat tcaagtgttg 3840
tcaaatcaat gtggaagaag gcagaggaaa acaatggtgg aacctgagaa ggacgtgttt 3900
ccgaatagtt gaacataact ggtttgagac cttcattgtt ttcatgattc tccttagtag 3960
tggtgctcgg catttgaaga tatatatatt gatcagcgaa agacgattaa gacgatgttg 4020
gaatatgctg acaaggtttt cacttacatt ttcattctgg aaatgcttct aaaatgggtg 4080
gcatatggct atcaaacata tttcaccaat gcctggtgtt ggctggactt cttaattgtt 4140

gatgtttcat tggtcagttt aacagcaaat gccttgggtt actcagaact tggagccatc 4200
aaatctctca ggacactaag agctctgaga cctctaagag ccttatctcg atttgaaggg 4260
atgagggtgg ttgtgaatgc ccttttagga gcaattccat ccatcatgaa tgtgcttctg 4320
gtttgtctta tattctggct aattttcagc atcatgggcg taaatttgtt tgctggcaaa 4380
ttctaccact gtattaacac cacaactggt gacaggtttg acatcgaaga cgtgaataat 4440
catactgatt gcctaaaact aatagaaaga aatgagactg ctcgatggaa aaatgtgaaa 4500
gtaaactttg ataatgtagg atttgggtat ctctctttgc ttcaagttgc cacattcaaa 4560
ggatggatgg atataatgta tgcagcagtt gattccagaa atgtggaact ccagcctaag 4620
tatgaagaaa gtctgtacat gtatctttac tttgttattt tcatcatctt tgggtccttc 4680
ttcaccttga acctgtttat tggtgtcatc atagataatt tcaaccagca gaaaaagaag 4740
tttggaggtc aagacatctt tatgacagaa gaacagaaga aatactataa tgcaatgaaa 4800
aaattaggat cgaaaaaacc gcaaaagcct atacctcgac caggaaacaa atttcaagga 4860
atggtctttg acttcgtaac cagacaagtt tttgacataa gcatcatgat tctcatctgt 4920
cttaacatgg tcacaatgat ggtggaaaca gatgaccaga gtgaatatgt gactaccatt 4980
ttgtcacgca tcaatctggt gttcattgtg ctatttactg gagagtgtgt actgaaactc 5040
atctctctac gccattatta ttttaccatt ggatggaata tttttgattt tgtggttgtc 5100
attctctcca ttgtaggtat gtttcttgcc gagctgatag aaaagtattt cgtgtcccct 5160
accctgttcc gagtgatccg tcttgctagg attggccgaa tcctacgtct gatcaaagga 5220
gcaaagggga tccgcacgct gctctttgct ttgatgatgt cccttcctgc gttgtttaac 5280
atcggcctcc tactcttcct agtcatgttc atctacgcca tctttgggat gtccaacttt 5340
gcctatgtta agagggaagt tgggatcgat gacatgttca actttgagac ctttggcaac 5400
agcatgatct gcctattcca aattacaacc tctgctggct gggatggatt gctagcaccc 5460
attctcaaca gtaagccacc cgactgtgac cctaataaag ttaaccctgg aagctcagtt 5520
aagggagact gtgggaaccc atctgttgga attttctttt ttgtcagtta catcatcata 5580
tccttcctgg ttgtggtgaa catgtacatc gcggtcatcc tggagaactt cagtgttgct 5640
actgaagaaa gtgcagagcc tctgagtgag gatgactttg agatgttcta tgaggtttgg 5700
gagaagtttg atcccgatgc aactcagttc atggaatttg aaaaattatc tcagtttgca 5760
gctgcgcttg aaccgcctct caatctgcca caaccaaaca aactccagct cattgccatg 5820
gatttgccca tggtgagtgg tgaccggatc cactgtcttg atatcttatt tgcttttaca 5880
aagcgggttc taggagagag tggagagatg gatgctctac gaatacagat ggaagagcga 5940
ttcatggctt ccaatccttc caaggtctcc tatcagccaa tcactactac tttaaaacga 6000
aaacaagagg aagtatctgc tgtcattatt cagcgtgctt acagacgcca ccttttaaag 6060
cgaactgtaa aacaagcttc ctttacgtac aataaaaaca aaatcaaagg tggggctaat 6120
cttcttataa aagaagacat gataattgac agaataaatg aaaactctat tacagaaaaa 6180
actgatctga ccatgtccac tgcagcttgt ccaccttcct atgaccgggt gacaaagcca 6240
attgtggaaa aacatgagca agaaggcaaa gatgaaaaag ccaaagggaa ataaatgaaa 6300
ataaataaaa ataattgggt gacaaattgt ttacagcctg tgaaggtgat gtatttttat 6360
caacaggact cctttaggag gtcaatgcca aactgactgt ttttacacaa atctccttaa 6420
ggtcagtgcc tacaataaga cagtgacccc ttgtcagcaa actgtgactc tgtgtaaagg 6480
ggagatgacc ttgacaggag gttactgttc tcactaccag ctgacactgc tgaagataag 6540
atgcacaatg gctagtcaga ctgtagggac cagtttcaag gggtgcaaac ctgtgatttt 6600
ggggttgttt aacatgaaac actttagtgt agtaattgta tccactgttt gcatttcaac 6660
tgccacattt gtcacatttt tatggaatct gttagtggat tcatcttttt gttaatccat 6720
gtgtttatta tatgtgacta tttttgtaaa cgaagtttct gttgagaaat aggctaagga 6780
cctctataac aggtatgcca cctgggggt atggcaacca catggccctc ccagctacac 6840
aaagtcgtgg tttgcatgag ggcatgctgc acttagagat catgcatgag aaaaagtcac 6900
aagaaaaaca aattcttaaa tttcaccata tttctgggag gggtaattgg gtgataagtg 6960
gaggtgcttt gttgatcttg ttttgcgaaa tccagcccct agaccaagta gattatttgt 7020

gggtaggcca gtaaatctta gcaggtgcaa acttcattca aatgtttgga gtcataaatg 7080
ttatgtttct ttttgttgta ttaaaaaaaa aacctgaata gtgaatattg cccctcaccc 7140
tccaccgcca gaagactgaa ttgaccaaaa ttactcttta taaatttctg ctttttcctg 7200
cactttgttt agccatcttc ggctctcagc aaggttgaca ctgtatatgt taatgaaatg 7260
ctatttatta tgtaaatagt cattttaccc tgtggtgcac gtttgagcaa acaaataatg 7320
acctaagcac agtatttatt gcatcaaata tgtaccacaa gaaatgtaga gtgcaagctt 7380
tacacaggta ataaaatgta ttctgtacca tttatagata gtttggatgc tatcaatgca 7440
tgtttatatt accatgctgc tgtatctggt ttctctcact gctcagaatc tcatttatga 7500
gaaaccatat gtcagtggta aagtcaagga aattgttcaa cagatctcat ttatttaagt 7560
cattaagcaa tagtttgcag cactttaaca gctttttggt tatttttaca ttttaagtgg 7620
ataacatatg gtatatagcc agactgtaca gacatgttta aaaaaacaca ctgcttaacc 7680
tattaaatat gtgtttagaa ttttataagc aaatataaat actgtaaaaa gtcactttat 7740
tttatttttc agcattatgt acataaatat gaagaggaaa ttatcttcag gttgatatca 7800
caatcacttt tcttactttc tgtccatagt acttttttcat gaaagaaatt tgctaaataa 7860
gacatgaaaa caagactggg tagttgtaga tttctgcttt ttaaattaca tttgctaatt 7920
ttagattatt tcacaatttt aaggagcaaa ataggttcac gattcatatc caaattatgc 7980
tttgcaattg gaaaagggtt taaaatttta tttatatttc tggtagtacc tgcactaact 8040
gaattgaagg tagtgcttat gttatttttg ttctttttt ctgacttcgg tttatgtttt 8100
catttctttg gagtaatgct gctctagttg ttctaaatag aatgtgggct tcataatttt 8160
tttttccaca aaaacagagt agtcaactta tatagtcaat tacatcagga cattttgtgt 8220
ttcttacaga agcaaaccat aggctcctct tttccttaaa actacttaga taaactgtat 8280
tcgtgaactg catgctggaa aatgctacta ttatgctaaa taatgctaac caacatttaa 8340
aatgtgcaaa actaataaag attacatttt ttatttta 8378

<210> 2
<211> 8378
<212> DNA
<213> Homo sapiens

<400> 2
tactgcagag gtctctggtg catgtgtgta tgtgtgcgtt tgtgtgtgtt tgtgtgtctg 60
tgtgttctgc cccagtgaga ctgcagccct tgtaaatact ttgacacctt ttgcaagaag 120
gaatctgaac aattgcaact gaaggcacat tgttatcatc tcgtctttgg gtgatgctgt 180
tcctcactgc agatggataa ttttcctttt aatcaggaat ttcatatgca gaataaatgg 240
taattaaaat gtgcaggatg acaagatgga gcaaacagtg cttgtaccac caggacctga 300
cagcttcaac ttcttcacca gagaatctct tgcggctatt gaaagacgca ttgcagaaga 360
aaaggcaaag aatcccaaac cagacaaaaa agatgacgac gaaaatggcc caaagccaaa 420
tagtgacttg gaagctggaa agaaccttcc atttatttat ggagacattc ctccagagat 480
ggtgtcagag cccctggagg acctggaccc ctactatatc aataagaaaa cttttatagt 540
attgaataaa gggaaggcca tcttccggtt cagtgccacc tctgccctgt acatttaac 600
tcccttcaat cctcttagga aaatagctat taagattttg gtacattcat tattcagcat 660
gctaattatg tgcactattt tgacaaactg tgtgtttatg acaatgagta accctcctga 720
ttggacaaag aatgtagaat acaccttcac aggaatatat acttttgaat cacttataaa 780
aattattgca aggggattct gtttagaaga ttttactttc cttcgggatc catggaactg 840
gctcgatttc actgtcatta catttgcgtt tgtaacagaa tttgtaaacc taggcaattt 900
ttcagctctt cgcactttca gagtcttgag agctttgaaa actatttcgg taattccagg 960
cctgaaaacc attgtgggag ccctgatcca gtctgtgaag aagctctcag atgtaatgat 1020

cctgactgtg ttctgtctga gcgtatttgc tctaattggg ctgcagctgt tcatgggcaa 1080
cctgaggaat aaatgtatac aatggcctcc caccaatgct tccttggagg aacatagtat 1140
agaaaagaat ataactgtga attataatgg tacacttata aatgaaactg tctttgagtt 1200
tgactggaag tcatatattc aagattcaag atatcattat ttcctggagg gtttttaga 1260
tgcactacta tgtggaaata gctctgatgc aggccaatgt ccagagggat atatgtgtgt 1320
gaaagctggt agaaatccca attatggcta cacaagcttt gataccttca gttgggcttt 1380
tttgtccttg tttcgactaa tgactcagga cttctgggaa aatctttatc aactgacatt 1440
acgtgctgct gggaaaacgt acatgatatt ttttgtattg gtcatttttct tgggctcatt 1500
ctacctaata aatttgatcc tggctgtggt ggccatggcc tacgaggaac agaatcaggc 1560
caccttggaa gaagcagaac agaaagaggc cgaatttcag cagatgattg aacagcttaa 1620
aaagcaacag gaggcagctc agcaggcagc aacggcaact gcctcagaac attccagaga 1680
gcccagtgca gcaggcaggc tctcagacag ctcatctgaa gcctctaagt tgagttccaa 1740
gagtgctaag gaaagaagaa atcggaggaa gaaaagaaaa cagaaagagc agtctggtgg 1800
ggaagagaaa gatgaggatg aattccaaaa atctgaatct gaggacagca tcaggaggaa 1860
aggttttcgc ttctccattg aagggaaccg attgacatat gaaaagaggt actcctcccc 1920
acaccagtct ttgttgagca tccgtggctc cctattttca ccaaggcgaa atagcagaac 1980
aagccttttc agctttagag ggcgagcaaa ggatgtggga tctgagaacg acttcgcaga 2040
tgatgagcca gcacctttga ggataacgag agccgtagag attccttgtt tgtgccccga 2100
cgacacggag agagacgcaa cagcaacctg agtcagacca gtaggtcatc ccggatgctg 2160
gcagtgtttc cagcgaatgg gaagatgcac agcactgtgg attgcaatgg tgtggtttcc 2220
ttggttggtg gaccttcagt tcctacatcg cctgttggac agcttctgcc agaggtgata 2280
atagataagc cagctactga tgacaatgga acaaccactg aaactgaaat gagaaagaga 2340
aggtcaagtt ctttccacgt ttccatggac tttctagaag atccttccca aaggcaacga 2400
gcaatgagta tagccagcat tctaacaaat acagtagaag aacttgaaga atccaggcag 2460
aaatgcccac cctgttggta taaattttcc aacatattct taatctggga ctgttctcca 2520
tattggttaa aagtgaaaca tgttgtcaac ctggttgtga tggacccatt tgttgacctg 2580
gccatcacca tctgtattgt cttaaatact cttttcatgg ccatggagca ctatccaatg 2640
acggaccatt tcaataatgt gcttacagta ggaaacttgg ttttcactgg gatctttaca 2700
gcagaaatgt ttctgaaaat tattgccatg gatccttact attatttcca agaaggctgg 2760
aatatctttg acggttttat tgtgacgctt agcctggtag aacttggact cgccaatgtg 2820
gaaggattat ctgttctccg ttcatttcga ttgctgcgag ttttcaagtt ggcaaaatct 2880
tggccaacgt taaatatgct aataaagatc atcggcaatt ccgtgggggc tctgggaaat 2940
ttaaccctcg tcttggccat catcgtcttc atttttgccg tggtcggcat gcagctcttt 3000
ggtaaaagct acaaagattg tgtctgcaag atcgccagtg attgtcaact cccacgctgg 3060
cacatgaatg acttcttcca ctccttcctg attgtgttcc gcgtgctgtg tggggagtgg 3120
atagagacca tgtgggactg tatggaggtt gctggtcaag ccatgtgcct tactgtcttc 3180
atgatggtca tggtgattgg aaacctagtg gtcctgaatc tctttctggc cttgcttctg 3240
agctcattta gtgcagacaa ccttgcagcc actgatgatg ataatgaaat gaataatctc 3300
caaattgctg tggataggat gcacaaagga gtagcttatg tgaaaagaaa aatatatgaa 3360
tttattcaac agtccttcat taggaaacaa aagattttag atgaaattaa accacttgat 3420
gatctaaaca acaagaaaga cagttgtatg tccaatcata cagcagaaat tgggaaagat 3480
cttgactatc ttaaagatgt aaatggaact acaagtggta taggaactgg cagcagtgtt 3540
gaaaaataca ttattgatga aagtgattac atgtcattca taaacaaccc cagtcttact 3600
gtgactgtac caattgctgt aggagaatct gactttgaaa atttaaacac ggaagacttt 3660
agtagtgaat cggatctgga agaaagcaaa gagaaactga atgaaagcag tagctcatca 3720
gaaggtagca ctgtggacat cggcgcacct gtagaagaac agcccgtagt ggaacctgaa 3780
gaaactcttg aaccagaagc ttgtttcact gaaggctgtg tacaaagatt caagtgttgt 3840
caaatcaatg tggaagaagg cagaggaaaa caatggtgga acctgagaag gacgtgtttc 3900

cgaatagttg aacataactg gtttgagacc ttcattgttt tcatgattct ccttagtagt 3960
ggtgctctgg catttgaaga tatatatatt gatcagcgaa agacgattaa gacgatgttg 4020
gaatatgctg acaaggtttt cacttacatt ttcattctgg aaatgcttct aaaatgggtg 4080
gcatatggct atcaaaatat ttcaccaatg cctggtgttg gctggacttc ttaattgttg 4140
atgtttcatt ggtcagttta acagcaaatg ccttgggtta ctcagaactt ggagccatca 4200
aatctctcag gacactaaga gctctgagac ctctaagagc cttatctcga tttgaaggga 4260
tgagggtggt tgtgaatgcc cttttaggag caattccatc catcatgaat gtgcttctgg 4320
tttgtcttat attctggcta attttcagca tcatgggcgt aaatttgttt gctggcaaat 4380
tctaccactg tattaacacc acaactggtg acaggtttga catcgaagac gtgaataatc 4440
atactgattg cctaaaacta atagaaagaa atgagactgc tcgatggaaa aatgtgaaag 4500
taaactttga taatgtagga tttgggtatc tctctttgct tcaagttgcc acattcaaag 4560
gatggatgga tataatgtat gcagcagttg attccagaaa tgtggaactc cagcctaagt 4620
atgaagaaag tctgtacatg tatctttact ttgttatttt catcatcttt gggtccttct 4680
tcaccttgaa cctgtttatt ggtgtcatca tagataattt caaccagcag aaaaagaagt 4740
ttggaggtca agacatcttt atgacagaag aacagaagaa atactataat gcaatgaaaa 4800
aattaggatc gaaaaaaccg caaaagccta tacctcgacc aggaaacaaa tttcaaggaa 4860
tggtctttga cttcgtaacc agacaagttt ttgacataag catcatgatt ctcatctgtc 4920
ttaacatggt cacaatgatg gtggaaacag atgaccagag tgaatatgtg actaccattt 4980
tgtcacgcat caatctggtg ttcattgtgc tatttactgg agagtgtgta ctgaaactca 5040
tctctctacg ccattattat tttaccattg gatggaatat ttttgatttt gtggttgtca 5100
ttctctccat tgtaggtatg tttcttgccg agctgataga aaagtatttc gtgtccccta 5160
ccctgttccg agtgatccgt cttgctagga ttggccgaat cctacgtctg atcaaaggag 5220
caaaggggat ccgcacgctg ctctttgctt tgatgatgtc ccttcctgcg ttgtttaaca 5280
tcggcctcct actcttccta gtcatgttca tctacgccat ctttgggatg tccaactttg 5340
cctatgttaa gagggaagtt gggatcgatg acatgttcaa ctttgagacc tttggcaaca 5400
gcatgatctg cctattccaa attacaacct ctgctggctg ggatggattg ctagcaccca 5460
ttctcaacag taagccaccc gactgtgacc ctaataaagt taaccctgga agctcagtta 5520
agggagactg tgggaaccca tctgttggaa ttttcttttt tgtcagttac atcatcatat 5580
ccttcctggt tgtggtgaac atgtacatcg cggtcatcct ggagaacttc agtgttgcta 5640
ctgaagaaag tgcagagcct ctgagtgagg atgactttga gatgttctat gaggtttggg 5700
agaagtttga tcccgatgca actcagttca tggaatttga aaaattatct cagtttgcag 5760
ctgcgcttga accgcctctc aatctgccac aaccaaacaa actccagctc attgccatgg 5820
atttgcccat ggtgagtggt gaccggatcc actgtcttga tatcttattt gcttttacaa 5880
agcgggttct aggagagagt ggagagatgg atgctctacg aatacagatg gaagagcgat 5940
tcatggcttc caatccttcc aaggtctcct atcagccaat cactactact ttaaaacgaa 6000
aacaagagga agtatctgct gtcattattc agcgtgctta cagacgccac cttttaaagc 6060
gaactgtaaa acaagcttcc tttacgtaca ataaaaacaa aatcaaaggt ggggctaatc 6120
ttcttataaa agaagacatg ataattgaca gaataaatga aaactctatt acagaaaaaa 6180
ctgatctgac catgtccact gcagcttgtc caccttccta tgaccgggtg acaaagccaa 6240
ttgtggaaaa acatgagcaa gaaggcaaag atgaaaaagc caaagggaaa taaatgaaaa 6300
taaataaaaa taattgggtg acaaattgtt tacagcctgt gaaggtgatg tatttttatc 6360
aacaggactc ctttaggagg tcaatgccaa actgactgtt tttacacaaa tctccttaag 6420
gtcagtgcct acaataagac agtgacccct tgtcagcaaa ctgtgactct gtgtaaaggg 6480
gagatgacct tgacaggagg ttactgttct cactaccagc tgacactgct gaagataaga 6540
tgcacaatgg ctagtcagac tgtagggacc agtttcaagg ggtgcaaacc tgtgattttg 6600
gggttgttta acatgaaaca ctttagtgta gtaattgtat ccactgtttg catttcaact 6660
gccacatttg tcacattttt atggaatctg ttagtggatt catcttttg ttaatccatg 6720
tgtttattat atgtgactat ttttgtaaac gaagtttctg ttgagaaata ggctaaggac 6780

ctctataaca ggtatgccac ctgggggtga tggcaaccac atggccctcc cagctacaca 6840
aagtcgtggt ttgcatgagg gcatgctgca cttagagatc atgcatgaga aaaagtcaca 6900
agaaaaacaa attcttaaat ttcaccatat ttctgggagg ggtaattggg tgataagtgg 6960
aggtgctttg ttgatcttgt tttgcgaaat ccagccccta gaccaagtag attatttgtg 7020
ggtaggccag taaatcttag caggtgcaaa cttcattcaa atgtttggag tcataaatgt 7080
tatgtttctt tttgttgtat taaaaaaaaa acctgaatag tgaatattgc ccctcaccct 7140
ccaccgccag aagactgaat tgaccaaaat tactctttat aaatttctgc tttttcctgc 7200
actttgttta gccatcttcg gctctcagca aggttgacac tgtatatgtt aatgaaatgc 7260
tatttattat gtaaatagtc attttaccct gtggtgcacg tttgagcaaa caaataatga 7320
cctaagcaca gtatttattg catcaaatat gtaccacaag aaatgtagag tgcaagcttt 7380
acacaggtaa taaaatgtat tctgtaccat ttatagatag tttggatgct atcaatgcat 7440
gtttatatta ccatgctgct gtatctggtt tctctcactg ctcagaatct catttatgag 7500
aaaccatatg tcagtggtaa agtcaaggaa attgttcaac agatctcatt tatttaagtc 7560
attaagcaat agtttgcagc actttaacag ctttttggtt atttttacat tttaagtgga 7620
taacatatgg tatatagcca gactgtacag acatgtttaa aaaaacacac tgcttaacct 7680
attaaatatg tgtttagaat tttataagca aatataaata ctgtaaaaag tcactttatt 7740
ttatttttca gcattatgta cataaatatg aagaggaaat tatcttcagg ttgatatcac 7800
aatcactttt cttactttct gtccatagta ctttttcatg aaagaaattt gctaaataag 7860
acatgaaaac aagactgggt agttgtagat ttctgctttt taaattacat ttgctaattt 7920
tagattattt cacaatttta aggagcaaaa taggttcacg attcatatcc aaattatgct 7980
ttgcaattgg aaaagggttt aaaattttat ttatatttct ggtagtacct gcactaactg 8040
aattgaaggt agtgcttatg ttatttttgt tctttttttc tgacttcggt ttatgttttc 8100
atttctttgg agtaatgctg ctctagattg ttctaaatag aatgtgggct tcataatttt 8160
tttttccaca aaaacagagt agtcaactta tatagtcaat tacatcagga cattttgtgt 8220
ttcttacaga agcaaaccat aggctcctct tttccttaaa actacttaga taaactgtat 8280
tcgtgaactg catgctggaa aatgctacta ttatgctaaa taatgctaac caacatttaa 8340
aatgtgcaaa actaataaag attacatttt ttatttta 8378

<210> 3
<211> 2009
<212> PRT
<213> Homo sapiens

<400> 3
Met Glu Gln Thr Val Leu Val Pro Pro Gly Pro Asp Ser Phe Asn Phe
1 5 10 15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Arg Arg Ile Ala Glu Glu
20 25 30

Lys Ala Lys Asn Pro Lys Pro Asp Lys Lys Asp Asp Asp Glu Asn Gly
35 40 45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
50 55 60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu

65 70 75 80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys Gly
85 90 95

Lys Ala Ile Phe Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
100 105 110

Pro Phe Asn Pro Leu Arg Lys Ile Ala Ile Lys Ile Leu Val His Ser
115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
130 135 140

Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
145 150 155 160

Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Ile Ala Arg
165 170 175

Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
180 185 190

Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val Asp
195 200 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
210 215 220

Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
225 230 235 240

Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
245 250 255

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
260 265 270

Leu Arg Asn Lys Cys Ile Gln Trp Pro Pro Thr Asn Ala Ser Leu Glu
275 280 285

Glu His Ser Ile Glu Lys Asn Ile Thr Val Asn Tyr Asn Gly Thr Leu
290 295 300

Ile Asn Glu Thr Val Phe Glu Phe Asp Trp Lys Ser Tyr Ile Gln Asp
305 310 315 320

Ser Arg Tyr His Tyr Phe Leu Glu Gly Phe Leu Asp Ala Leu Leu Cys

325 330 335

Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Met Cys Val
340 345 350

Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr Phe
355 360 365

Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Phe Trp
370 375 380

Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr Met
385 390 395 400

Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Ile Asn
405 410 415

Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn Gln Ala
420 425 430

Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met Ile
435 440 445

Glu Gln Leu Lys Lys Gln Gln Glu Ala Ala Gln Gln Ala Ala Thr Ala
450 455 460

Thr Ala Ser Glu His Ser Arg Glu Pro Ser Ala Ala Gly Arg Leu Ser
465 470 475 480

Asp Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala Lys Glu
485 490 495

Arg Arg Asn Arg Arg Lys Lys Arg Lys Gln Lys Glu Gln Ser Gly Gly
500 505 510

Glu Glu Lys Asp Glu Asp Glu Phe Gln Lys Ser Glu Ser Glu Asp Ser
515 520 525

Ile Arg Arg Lys Gly Phe Arg Phe Ser Ile Glu Gly Asn Arg Leu Thr
530 535 540

Tyr Glu Lys Arg Tyr Ser Ser Pro His Gln Ser Leu Leu Ser Ile Arg
545 550 555 560

Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Thr Ser Leu Phe Ser
565 570 575

Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp Phe Ala Asp

580 585 590

Asp Glu His Ser Thr Phe Glu Asp Asn Glu Ser Arg Arg Asp Ser Leu
595 600 605

Phe Val Pro Arg Arg His Gly Glu Arg Arg Asn Ser Asn Leu Ser Gln
610 615 620

Thr Ser Arg Ser Ser Arg Met Leu Ala Val Phe Pro Ala Asn Gly Lys
625 630 635 640

Met His Ser Thr Val Asp Cys Asn Gly Val Val Ser Leu Val Gly Gly
645 650 655

Pro Ser Val Pro Thr Ser Pro Val Gly Gln Leu Leu Pro Glu Val Ile
660 665 670

Ile Asp Lys Pro Ala Thr Asp Asp Asn Gly Thr Thr Thr Glu Thr Glu
675 680 685

Met Arg Lys Arg Arg Ser Ser Ser Phe His Val Ser Met Asp Phe Leu
690 695 700

Glu Asp Pro Ser Gln Arg Gln Arg Ala Met Ser Ile Ala Ser Ile Leu
705 710 715 720

Thr Asn Thr Val Glu Glu Leu Glu Glu Ser Arg Gln Lys Cys Pro Pro
725 730 735

Cys Trp Tyr Lys Phe Ser Asn Ile Phe Leu Ile Trp Asp Cys Ser Pro
740 745 750

Tyr Trp Leu Lys Val Lys His Val Val Asn Leu Val Val Met Asp Pro
755 760 765

Phe Val Asp Leu Ala Ile Thr Ile Cys Ile Val Leu Asn Thr Leu Phe
770 775 780

Met Ala Met Glu His Tyr Pro Met Thr Asp His Phe Asn Asn Val Leu
785 790 795 800

Thr Val Gly Asn Leu Val Phe Thr Gly Ile Phe Thr Ala Glu Met Phe
805 810 815

Leu Lys Ile Ile Ala Met Asp Pro Tyr Tyr Tyr Phe Gln Glu Gly Trp
820 825 830

Asn Ile Phe Asp Gly Phe Ile Val Thr Leu Ser Leu Val Glu Leu Gly

835 840 845

Leu Ala Asn Val Glu Gly Leu Ser Val Leu Arg Ser Phe Arg Leu Leu
850 855 860

Arg Val Phe Lys Leu Ala Lys Ser Trp Pro Thr Leu Asn Met Leu Ile
865 870 875 880

Lys Ile Ile Gly Asn Ser Val Gly Ala Leu Gly Asn Leu Thr Leu Val
885 890 895

Leu Ala Ile Ile Val Phe Ile Phe Ala Val Val Gly Met Gln Leu Phe
900 905 910

Gly Lys Ser Tyr Lys Asp Cys Val Cys Lys Ile Ala Ser Asp Cys Gln
915 920 925

Leu Pro Arg Trp His Met Asn Asp Phe Phe His Ser Phe Leu Ile Val
930 935 940

Phe Arg Val Leu Cys Gly Glu Trp Ile Glu Thr Met Trp Asp Cys Met
945 950 955 960

Glu Val Ala Gly Gln Ala Met Cys Leu Thr Val Phe Met Met Val Met
965 970 975

Val Ile Gly Asn Leu Val Val Leu Asn Leu Phe Leu Ala Leu Leu Leu
980 985 990

Ser Ser Phe Ser Ala Asp Asn Leu Ala Ala Thr Asp Asp Asp Asn Glu
995 1000 1005

Met Asn Asn Leu Gln Ile Ala Val Asp Arg Met His Lys Gly Val Ala
1010 1015 1020

Tyr Val Lys Arg Lys Ile Tyr Glu Phe Ile Gln Gln Ser Phe Ile Arg
1025 1030 1035 1040

Lys Gln Lys Ile Leu Asp Glu Ile Lys Pro Leu Asp Asp Leu Asn Asn
1045 1050 1055

Lys Lys Asp Ser Cys Met Ser Asn His Thr Ala Glu Ile Gly Lys Asp
1060 1065 1070

Leu Asp Tyr Leu Lys Asp Val Asn Gly Thr Thr Ser Gly Ile Gly Thr
1075 1080 1085

Gly Ser Ser Val Glu Lys Tyr Ile Ile Asp Glu Ser Asp Tyr Met Ser

1090 1095 1100

Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile Ala Val Gly
1105 1110 1115 1120

Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Asp Phe Ser Ser Glu Ser
1125 1130 1135

Asp Leu Glu Glu Ser Lys Glu Lys Leu Asn Glu Ser Ser Ser Ser Ser
1140 1145 1150

Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Val Glu Glu Gln Pro Val
1155 1160 1165

Val Glu Pro Glu Glu Thr Leu Glu Pro Glu Ala Cys Phe Thr Glu Gly
1170 1175 1180

Cys Val Gln Arg Phe Lys Cys Cys Gln Ile Asn Val Glu Glu Gly Arg
1185 1190 1195 1200

Gly Lys Gln Trp Trp Asn Leu Arg Arg Thr Cys Phe Arg Ile Val Glu
1205 1210 1215

His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu Leu Ser Ser
1220 1225 1230

Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Asp Gln Arg Lys Thr Ile
1235 1240 1245

Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr Ile Phe Ile
1250 1255 1260

Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Tyr Gln Thr Tyr Phe
1265 1270 1275 1280

Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp Val Ser Leu
1285 1290 1295

Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr Ser Glu Leu Gly Ala Ile
1300 1305 1310

Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro Leu Arg Ala Leu Ser
1315 1320 1325

Arg Phe Glu Gly Met Arg Val Val Val Asn Ala Leu Leu Gly Ala Ile
1330 1335 1340

Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe Trp Leu Ile

1345 1350 1355 1360

Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe Tyr His Cys
1365 1370 1375

Ile Asn Thr Thr Thr Gly Asp Arg Phe Asp Ile Glu Asp Val Asn Asn
1380 1385 1390

His Thr Asp Cys Leu Lys Leu Ile Glu Arg Asn Glu Thr Ala Arg Trp
1395 1400 1405

Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Phe Gly Tyr Leu Ser
1410 1415 1420

Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala
1425 1430 1435 1440

Ala Val Asp Ser Arg Asn Val Glu Leu Gln Pro Lys Tyr Glu Glu Ser
1445 1450 1455

Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
1460 1465 1470

Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln
1475 1480 1485

Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
1490 1495 1500

Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
1505 1510 1515 1520

Lys Pro Ile Pro Arg Pro Gly Asn Lys Phe Gln Gly Met Val Phe Asp
1525 1530 1535

Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
1540 1545 1550

Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Ser Glu Tyr
1555 1560 1565

Val Thr Thr Ile Leu Ser Arg Ile Asn Leu Val Phe Ile Val Leu Phe
1570 1575 1580

Thr Gly Glu Cys Val Leu Lys Leu Ile Ser Leu Arg His Tyr Tyr Phe
1585 1590 1595 1600

Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile

1605 1610 1615

Val Gly Met Phe Leu Ala Glu Leu Ile Glu Lys Tyr Phe Val Ser Pro
1620 1625 1630

Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
1635 1640 1645

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
1650 1655 1660

Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val
1665 1670 1675 1680

Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys
1685 1690 1695

Arg Glu Val Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn
1700 1705 1710

Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
1715 1720 1725

Leu Leu Ala Pro Ile Leu Asn Ser Lys Pro Pro Asp Cys Asp Pro Asn
1730 1735 1740

Lys Val Asn Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
1745 1750 1755 1760

Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
1765 1770 1775

Val Val Asn Met Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala
1780 1785 1790

Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe
1795 1800 1805

Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Met Glu
1810 1815 1820

Phe Glu Lys Leu Ser Gln Phe Ala Ala Ala Leu Glu Pro Pro Leu Asn
1825 1830 1835 1840

Leu Pro Gln Pro Asn Lys Leu Gln Leu Ile Ala Met Asp Leu Pro Met
1845 1850 1855

Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr

1860 1865 1870

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
1875 1880 1885

Met Glu Glu Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Gln
1890 1895 1900

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Val
1905 1910 1915 1920

Ile Ile Gln Arg Ala Tyr Arg Arg His Leu Leu Lys Arg Thr Val Lys
1925 1930 1935

Gln Ala Ser Phe Thr Tyr Asn Lys Asn Lys Ile Lys Gly Gly Ala Asn
1940 1945 1950

Leu Leu Ile Lys Glu Asp Met Ile Ile Asp Arg Ile Asn Glu Asn Ser
1955 1960 1965

Ile Thr Glu Lys Thr Asp Leu Thr Met Ser Thr Ala Ala Cys Pro Pro
1970 1975 1980

Ser Tyr Asp Arg Val Thr Lys Pro Ile Val Glu Lys His Glu Gln Glu
1985 1990 1995 2000

Gly Lys Asp Glu Lys Ala Lys Gly Lys
2005

<210> 4
<211> 1246
<212> DNA
<213> Homo sapiens

<400> 4
mtvvgdsntr saarrakakn kdkkdddngk nsdagknygd mvsddyynkk tvnkgkarsa 60
tsaytnrkak vhssmmcttn cvmtmsndwt knvyttgyts kargcdtrdw nwdtvtavtv 120
ngnsartrvr aktsvgktvg asvkksdvmt vcsvagmgnr nkcwtnashs kntvnyngtn 180
tvdwksydsr yhygdacgns sdagcgymcv kagrnnygyt sdtswasrmt dwnytraagk 240
tymvvgsyna vvamaynata kamkkaaaat atashsrsaa grsdsssask ssksakrrnr 300
rkkrkksggk ddkssdsrrk grsgnrtykr ysshssrgss rrnsrtssrg rakdvgsnda 360
ddhstdnsrr dsvrrhgrrn snstsrssrm avangkmhst vdcngvvsvg gsvtsvgvdk 420
atddngtttt mrkrrssshv smddsrrams astntvsrkc cwyksnwdcs ywkvkhvvnv 480
vmdvdatcvn tmamhymtdh nnvtvgnvtg tamkamdyyy gwndgvtsvg anvgsvrsrr 540
vkakswtnmk gnsvgagntv avavvgmgks ykdcvckasd crwhmndhsv rvcgwtmwdc 600
mvagamctvm mvmvgnvvna sssadnaatd ddnmnnavdr mhkgvayvkr kysrkkdkdd 660
nnkkdscmsn htagkddykd vngttsggtg ssvkydsdym snnstvtvav gsdnntdsss 720

dskknsssss gstvdgavvv tactgcvrkc cnvgrgkwwn rrtcrvhnwt vmssgaadyd 780
rktktmyadk vtymkwvayg ytytnawcwd vdvsvstana gysgaksrtr arrasrgmrv 840
vvnagasmnv vcwsmgvnag kyhcntttgd rddvnnhtdc krntarwknv kvndnvggys 900
vatkgwmdmy aavdsrnvky symyyvgstn gvdnnkkkgg dmtkkyynam kkgskkkrgn 960
kgmvdvtrvd smcnmvtmmv tddsyvttsr nvvtgcvksr hyytgwndvv vsvgmakyvs 1020
trvrargrrk gakgrtamms angvmyagms nayvkrvgdd mntgnsmctt sagwdgansk 1080
dcdnkvngss vkgdcgnsvg vsysvvvnmy avnsvatsas ddmyvwkdda tmksaaannk 1140
amdmvsgdrh cdatkrvgsg mdarmrmasn skvsytttkr kvsavrayrr hkrtvkasty 1200
nknkkggank dmdrnnstkt dtmstaacsy drvtkvkhgk dkakgk 1246

<210> 5
<211> 850
<212> DNA
<213> Homo sapiens

<400> 5
ctaaaataat gctaaagttt ttcaagtact acttgaaaat agctatattt actttcaaac 60
cttttcctct ttgagtcatt aggttcatga tattatatag caatagggaa tgaaagagaa 120
gcaaggagaa gcaatactgg gagattacag agaagaaagg aaaaaaggct gagagaaaag 180
aggttgagga agaaatcata aatctggatt gtgagaaagt gtttaatatt tagccactag 240
atggcgatgt aatgtaaggt gctgtcttga ctttttttt ttttttttga aacaagctat 300
ttgctgattt gtattaggta ccatagagtg aggcgaggat gaagccgaga agatactgca 360
gaggtctctg gtgcatgtgt gtatgtgtgc gtttgtgtgt gtttgtgtgt ctgtgtgttc 420
tgccccagtg agactgcagc ccttgtaaat actttgacac cttttgcaag aaggaatctg 480
aacaattgca actgaaggca cattgttatc atctcgtctt tgggtgatgc tgttcctcac 540
tgcagatgga taattttcct tttaatcagg taagccatct aattgtttca tcttgatttt 600
aagtttattc attccagtta ttcctttgga aaaagagtcc atggaaattc agtttgggca 660
gagcaggaag tccatttttg tatgtgtatt cagaccaact gtcccccctcc tccctctcct 720
cctcttcttg tcccctcccc cgcgccctcc tctctcaacc ttccatgaac tgaaatcagg 780
tttgttttgc agttcagcat tttgatagaa gatgggattc tttggcctga aatagcttgg 840
catctggcca 850

<210> 6
<211> 483
<212> DNA
<213> Homo sapiens

<400> 6
acatctctta gtcctctctt aaatatctgt attcctttta ttttaggaat ttcatatgca 60
gaataaatgg taattaaaat gtgcaggatg acaagatgga gcaaacagtg cttgtaccac 120
caggacctga cagcttcaac ttcttcacca gagaatctct tgcggctatt gaaagacgca 180
ttgcagaaga aaaggcaaag aatcccaaac cagacaaaaa aagatgacga cgaaaaatgg 240
cccaaagcaa atagtgactt ggaagctgga aagaaccttc catttattta tggagacatt 300
cctccagaga tggtgtcaga gcccctggag gacctggacc cctactatat caataagaaa 360
gtgagtgttt tttttatcag gcatattttt gctgctaatt gcctactgca ttccttggac 420
tgttgtagca ccaacacatg ccaatagcac aaatctagta tctctgttag aatgaacaca 480

ttt 483

<210> 7
<211> 497
<212> DNA
<213> Homo sapiens

<400> 7
taagaagaga tccagtgaca gtttgttttc atggggcact ttaggaaatt gtgattgtgc 60
tggtttctca tttaacttta caataattta ttatgacaag taacagaaag tagataacag 120
agtttaagtg gtttatactt tcatacttct atgttgtgtt cctgtcttac agacttttat 180
agtattgaat aaagggaagg ccatcttccg gttcagtgcc acctctgccc tgtacatttt 240
aactcccttc aatcctctta ggaaaatagc tattaagatt ttggtacatt catatccttt 300
ttcaagtgat taatattaac tatttgtaca tgatctgtaa gcactttata gctaaatatc 360
aaattaagtt gggaaatgtc catattatat aggtttcatc actctcattt tgcatctttg 420
tcatattagc ctcattctta aagttcatta atcacataga cattactgaa acatgtactc 480
tttaacattt tatatat 497

<210> 8
<211> 501
<212> DNA
<213> Homo sapiens

<400> 8
tcatatacat tacctcattt aatctataca aatactcagt gaaggtgata ttattaccca 60
cattttacac atgaagaaat tgaaatgtaa ggagattaga agacttgccc acaatgcatt 120
tatccctgaa ttttggctaa gctgcagttt gggcttttca atgttagctt tttgtaatat 180
aacacttgga ttttgatttt cttttgtgtg ttccttaaca ataacctaca ttattcagca 240
tgctaattat gtgcactatt ttgacaaact gtgtgtttat gacaatgagt aaccctcctg 300
attggacaaa gaatgtagag taagttcaac ttatattttt aataacatat atacattygg 360
gattytgaaa ctgtgtctta atgtagtctt aaaataaaac tgaagagcat tttattaaag 420
tcattcctag acaaaattac gcagcaagag gacaatgctc attggccctc aggcctgctg 480
gcgttatact gattatcact c 501

<210> 9
<211> 563
<212> DNA
<213> Homo sapiens

<400> 9
gctaaataga tttcatatac cttgtatttc tcacactact cttaagacac tttacgaaac 60
aactctttgt gttaggaagc tgaatttaaa tttagggcta cgtttcattt gtatgaaatt 120
aaaatccatc tgcttagttt tctttttttag tatttatcta ttccactgat ggagtgataa 180
gaaattggta tgctatgaaa aaacactgtt actttatcaa atttttgga tgcttgtttt 240
cagatacacc ttcacaggaa tatatacttt tgaatcactt ataaaaatta ttgcaagggg 300

attctgttta gaagatttta ctttccttcg ggatccatgg aactggctcg atttcactgt 360
cattacattt gcgtaagtgc ctttbytgaa actttaagag agaacatagt ttggttttcc 420
atcagtgctt atgcttttaa gaataggttt gctttacctg tagaatattt ttgtgtgatt 480
tatacattca aactctggat ttcaatttag cacaacaaag gtctaagtgg aatttcacta 540
tagcatgaag gctttgcagt agt 563

<210> 10
<211> 253
<212> DNA
<213> Homo sapiens

<400> 10
cttataagcc catgcagtaa tataaatcct gctaaaatct tgaataattc tgatttaatt 60
ctacaggttt gtaacagaat ttgtaaacct aggcaatttt tcagctcttc gcactttcag 120
agtcttgaga gctttgaaaa ctatttcggt aattccaggt aagaagtgat tagagtaaag 180
gataggctct ttgtacctac agctttttct ttgtgtcctg tttttgtgtt tgtgtgtgaa 240
ctcccgctta cag 253

<210> 11
<211> 340
<212> DNA
<213> Homo sapiens

<400> 11
gtaagaagtg attagagtaa aggataggct ctttgtacct acagcttttt ctttgtgtcc 60
tgtttttgtg tttgtgtgtg aactcccgct tacaggtacg tcacagagtt tgtggacctg 120
ggcaatgtct cggcattgag aacattcaga gttctccgag cattgaagac gatttcagtc 180
attccaggtg agagcaaggt tagataatga gacggaccca tcatgtgatt cagcatcctt 240
ctctgcttga cattcagttt tacagaaaat caggaatcat aagactaggt gttcaaagaa 300
atgattatta tgttagacat agcttatcag cctggagtta 340

<210> 12
<211> 409
<212> DNA
<213> Homo sapiens

<400> 12
cacgcgtgct tagccctcat agtaatagcc tcctaccttc aggcctgaaa accattgtgg 60
gagccctgat ccagtctgtg aagaagctct cagatgtaat gatcctgact gtgttctgtc 120
tgagcgtatt tgctctaatt gggctgcagc tgttcatggg caacctgagg aataaatgta 180
tacaatggcc tcccaccaat gcttccttgg aggaacatag tatagaaaag aatataactg 240
tgaattataa tggtacactt ataaatgaaa ctgtctttga gtttgactgg aagtcatata 300
ttcaagattc aagtaagaat tattgttatg tacatttcct taaaaagtag aattggattg 360
tttgtaacac aaaggataaa tacttgaggg gctggatatc ccattttac 409

<210> 13
<211> 266
<212> DNA
<213> Homo sapiens

<400> 13
cgcgcaaata cttgtgcctt tgaatgaata atatatttaa aattactcaa taaacttaaa 60
agtagaacct gaccttcctg ttctctttga gtgtttttaa caatgcaaat gttcagcata 120
cgactttctt ttttcaaaca ggatatcatt atttcctgga gggtttttta gatgcactac 180
tatgtggaaa tagctctgat gcagggtaag tcaatattgt gtgcatctgt gtatattgta 240
tgtacacaat acatatgtgt atcttt 266

<210> 14
<211> 604
<212> DNA
<213> Homo sapiens

<400> 14
aggtgttgaa aatgcaaatt atcaacaaaa attattttgt aaaatattat tagaaatgct 60
gcaccatatt ttaatgatga caccaagtag ctaataagac tatatgcagt caaaagttgg 120
gaaatagatt agttacttat ttgtcaaact tttattttga aataccaaat ctttctgact 180
aggcaatatc atagcatagt atcagagtaa aaaggcagca gaacgacttg taatactttc 240
ttttacccca cttgcagcca atgtccagag ggatatatgt gtgtgacagc tggtagaaat 300
cccaattatg gctacacaag ctttgatacc ttcagttggg ctttttttgtc cttgtttcga 360
ctaatgactc aggacttctg ggaaaatctt tatcaactgg tgagaactaa agagccacac 420
tctccattta agtaaaagta tacaagaaaa ccaattgagt tatgaaatta aaaccggatg 480
ataatatagt agaaagagca gaacttgaca cgagacttga gttcctctat cctattgatt 540
ataacacata ctgagcagag tgatgccaag gattgcaatt ctctcccatt tcttcttggc 600
tcaa 604

<210> 15
<211> 378
<212> DNA
<213> Homo sapiens

<400> 15
ttatatctga gttttgctag ccacatgagt aaattgaaag ttgagcaccc ttagtgaata 60
atattgggaa ataattctga tatttttgtt tgcagacatt acgtgctgct gggaaaacgt 120
acatgatatt ttttgtattg gtcatttttct tgggctcatt ctacctaata aatttgatcc 180
tggctgtggt ggccatggcc tacgaggaac agaatcaggc caccttggaa gaagcagaac 240
agaaagaggc cgaatttcag cagatgattg aacagcttaa aaagcaacag gaggcagctc 300
aggtaagctg ccctgctcat ggcactgacc tttatcgtct gatgtactat atgagagaag 360
tagtctagag cgtgtgat 378

<210> 16
<211> 845
<212> DNA
<213> Homo sapiens

<400> 16
caaccctaat taaataccaa tttttaaagt aaatcaaatc ccaaaaagta atgaatttat 60
tttcttgttg atacatgttg gatatttttg aatacgtggt ctgtggagca ttaacagaga 120
cataataaat gttaccatgg agcaaactaa attatctcca aaagccttca ttaggtagaa 180
agaaaaaaaa aatctcctct tatacttgca gagaatcttc tctgtgagat gatcttcagt 240
cagttcaata tatttttaa aagccatgca aatacttcag ccctttcaaa gaaagataca 300
gtctcttcag gtgctatgtt aaaatcattt ctcttcaata tagcaggcag caacggcaac 360
tgcctcagaa cattccagag agcccagtgc agcaggcagg ctctcagaca gctcatctga 420
agcctctaag ttgagttcca agagtgctaa ggaaagaaga aatcggagga agaaaagaaa 480
acagaaagag cagtctggtg gggaagagaa agatgaggat gaattccaaa aatctgaatc 540
tgaggacagc atcaggaggw aaggttttcg cttctccatt gaagggaacc ggttgacata 600
tgaaaagagg tactcctccc cacaccaggt atggcactgc tgagtttact gatgcatggt 660
tgaaaattaa aacatgggag agagggggag atttagaaaa tggactcagg aatttttatc 720
aactgaatca accactgttg tgttatattt aaacccatcc cttcttcaca tagttatgca 780
aaaactttac tccacagata tgtaagtcta cagctcggtg tagttaagat aacaccaagt 840
tgaca 845

<210> 17
<211> 965
<212> DNA
<213> Homo sapiens

<400> 17
cattgccata ttctaaggat gtttcccttt gaacttgaga aatggtcgtt cagggtgtgt 60
gtgtatgtgt gtgtgtgtgt gtttcaatat gttaaggttg caatctatct cctcattctt 120
taatcccaag ggctagaaac tttcttttat caaggtaatt taatttaatg tgaatgcaca 180
taaaatgaga atgataatca aaaggaatga accatattct gttatgaatg ctgaaatctc 240
cttctacata atcttgcaaa atgaaatcac attcaaatgt ccatattaat atgactctat 300
ttgtbtgctc tttcaaactt ctagtctttg ttgagcatcc gtggctccct attttcacca 360
aggcgaaata gcagaacaag ccttttcagc tttagagggc gagcaaagga tgtgggatct 420
gagaacgact tcgcagatga tgagcacagc acctttgagg ataacgagag ccgtagagat 480
tccttgtttg tgccccgacg acacggagag agacgcaaca gcaacctgag tcagaccagt 540
aggtcatccc ggatgctggc agtgtttcca gcgaatggga agatgcacag cactgtggat 600
tgcaatggtg tgggttcctt ggttggtgga ccttcagttc ctacatcgcc tgttggacag 660
cttctgccag aggtgataat agataagcca gctactgatg acaatgtaag gaagtyttaa 720
atagttcagg catggctggc tcactattgc tgcaccagcc agtgtgtcta cagaacggca 780
accttgagaa tgattcctgg ttggtcacgc tgtgaatgca cctgcatctt gtaatatctt 840
tgatagacta accaactaaa acttaaaacc ttagcagtcg cctgcacaaa cctgaatgca 900
tttacttatt aaaagtgcta aggattgatt agacacaata attactgcct ccagttggag 960
gattt 965

<210> 18
<211> 641
<212> DNA
<213> Homo sapiens

<400> 18
aagagtttta tcaactatat taaaattatt ttgtatttta taaaattatg aaatcaggaa 60
gttaacatct tggtttttgc tgtatgacta aatggttaac agtttgaaca ttccaggcta 120
atgatacaat aagtcagaaa tatctgccat caccaattga atatgaaagt gcatgatgca 180
tgtgtttcat gaaattcact gtgtcaccat ttggttgttt gcttgtcata ttgctcaaat 240
taattgttta atgcattagc attttttttt acagggaaca accactgaaa ctgaaatgag 300
aaagagaagg tcaagttctt tccacgtttc catggacttt ctagaagatc cttcccaaag 360
gcaacgagca atgagtatag ccagcattct aacaaataca gtagaaggtt ggtaacaaat 420
tctatttttcg tttcaattat tttcaccaaa cttatattgt ctcatttcaa acaaatatat 480
ttgtgagttg ggaatagtgc attctaatga aaagacagtc taattcaaga gctgttattt 540
cttatatcta ctcagatatt ctagaagcct taacaattta ttttaaaatg agtgatattg 600
ggactaagac tgttttccta actgtgtagc aactctttga a 641

<210> 19
<211> 818
<212> DNA
<213> Homo sapiens

<400> 19
gtgaggcggc acatgaaaga ccacccattt aacctgaggc caagtgctga gccacaatgg 60
cagtgcataa gacaaaaaac tacccattgt tacctgggcc ctatgtgtgt gtctgatgaa 120
ataaccttgg gaggtttaga gtaaactgta attttttaa caagtacaaa aaagggtgtc 180
tctgtaacaa aaatgtgttg attactgaaa ataagtttag tggatatgaa ataaatgtgt 240
gtgtataaag tawacctttt ggtgggtctt ttttttttt ttcttaatct agaacttgaa 300
gaatccaggc agaaatgccc accctgttgg tataaatttt ccaacatatt cttaatctgg 360
gactgttctc catattggtt aaaagtgaaa catgttgtca acctggttgt gatggaccca 420
tttgttgacc tggccatcac catctgtatt gtcttaaata ctcttttcat ggccatggag 480
cactatccaa tgacggacca tttcaataat gtgcttacag taggaaactt ggtaagcata 540
ttggaaggta aatgtgttta gtcttcaaat tttctgcttg aaaaactgtt tacatttaat 600
tgtgtatagc agtctttcaa ccatccttca tgcttcctgg cccctgcaaa atcgcaatta 660
tatttagctg gctatactct actttttttgc caaaaataat caccccttaat gtgctcacaa 720
aaactgagaa aggcataggc ctacagcact acttgaaaag tcaacagcaa tatttataat 780
ttttcaggat ccagaagtag ctcatagatt aagaacat 818

<210> 20
<211> 645
<212> DNA
<213> Homo sapiens

<400> 20
caagccattt cacccatctg aagacctcag tttccttatc tgtaaagtaa taattgtata 60

ttatctactt cgcgtttcca caaggataaa attaaataat gtatatgawa gtctttcatc 120
aactacaaat tgccatacaa atttaagtta gtaatagaat cattgtggga aaatagcata 180
agcattatgt tctaagagca aatcttatgt catgtatgtt attatctggt ggaattagat 240
taattttgtt ttgatcttag gttttcactg ggatctttac agcagaaatg tttctgaaaa 300
ttattgccat ggatccttac tattatttcc aagaaggctg gaatatcttt gacggtttta 360
ttgtgacgct tagcctggta gaacttggac tcgccaatgt ggaagggtta tctgttctcc 420
gttcatttcg attggtaaaa aaaaaaaaaa aaggaaccaa attcaaaaac ctttctaaca 480
ttcagggttc ttgcatagca ttgtcatagt ttttttgcca cacaaccatt aggcattgta 540
agtttttctg taacatttgc attgtcaaaa acttttccta catgggaata attctcaatt 600
attaggttac cttagttcaa gggcwaggtc ggaaaggtaa cggtt 645

<210> 21
<211> 829
<212> DNA
<213> Homo sapiens

<400> 21
gaattctaat gaccatttct aggtaaagct caatatatat aatgctttta agaatcatac 60
aaatatatat taatctttca ttttccagct gcgagatttc aagttggcaa aatcttggcc 120
aacgttaaat atgctaataa agatcatcgg caattccgtg ggggctctgg gaaatttaac 180
cctcgtcttg gccatcatcg tcttcatttt tgccgtggtc ggcatgcagc tctttggtaa 240
aagctacaaa gattgtgtct gcaagatcgc cagtgattgt caactcccac gctggcacat 300
gaatgacttc ttccactcck hcctgattgt gttccgcgtg ctgtgtgggg agtggataga 360
gaccatgtgg gactgtatgg aggttgctgg tcaagccatg tgccttactg tcttcatgat 420
ggtcatggtg attggaaacc tagcggtatg tacccactta agatatgcat tttggaaata 480
caccagcatg gcacatgtat acatatgtaa ctaacctgca cattgtgcac atgtacccta 540
aaacttaaag tataataaaa aaaaagagta taatttaatg gtgactgttt tgtcaaaaag 600
aaaaacaaac tatgattatt ggtttaaaag tccattacct tggatatatt atcactttaa 660
caacacagca atatabcagt gcccctgcat tttttatacc aaattctatt ttgtcagtca 720
ctttatcaca ttttttatgt gaattacaat agagtatcat attgagatga gcctaaaagg 780
atgtgctggg accattttat aaattcagag ccaaggaaga gagaagtct 829

<210> 22
<211> 909
<212> DNA
<213> Homo sapiens

<400> 22
gaattctcgt attgtacaca tataaatctg ttttcttcta ctcatacaat tttagagtta 60
acaaaacctt agattagctc attcaatttc actttacgaa tgggagaact tgagagcaac 120
agaaatcatg tctttgtcca aggatgtgct attgagccag tcacaaattc agatcaccca 180
tcttctaatc actatgctgt ggtgtttcct tctcatcaag ttttagaact tagagttttt 240
tccacactta aaagaaagaa taagtgattg taatctgctc ttccctacat tggtgtaaaa 300
ttataatcat gtttttgttg tttttaaggt cctgaatctc tttctggcct tgcttctgag 360
ctcatttagt gcagacaacc ttgcagccac tgatgatgat aatgaaatga ataatctcca 420
aattgctgtg gataggatgc acaaaggagt agcttatgtg aaaagaaaaa tatatgartt 480

tattcaacag tccttcatta ggaaacaaaa gattttagat gaaattaaac cacttgatga 540
tctaaacaac aagaaagaca gttgtatgtc caatcataca gcagaaattg ggaaagatct 600
tgactatctt aaagatgtaa atggaactac aagtggtata ggaactggca gcagtgttga 660
aaaatacatt attgatgaaa gtgattacat gtcattcata aacaacccca gtcttactgt 720
gactgtacca attgctgtag gagaatctga ctttgaaaat ttaaacacgg aagactttag 780
tagtgaatcg gatctggaag aaagcaaaga ggtaagattc tataggtgtg ggtaggtatg 840
aatacatata catatataca tatacacaca tacagatgay cctcagctta atgatgtttt 900
tacttaaga 909

<210> 23
<211> 516
<212> DNA
<213> Homo sapiens

<400> 23
aagcttacat tgtgaattat ggtaaaaggg ttagcacaga caatgatttt cttatttctt 60
ccccttattc aatctctctt tttctctaaa aatatctcta cctcaagaag aataaaaaac 120
aaattcatag taataatcct tcttggcagg caacttatta ccaaaattaa ggactttact 180
ttctatgtcc atctcactta cagaaactga atgaaagcag tagctcatca gaaggtagca 240
ctgtggacat cggcgcacct gtagaagaac agcccgtagt ggaacctgaa gaaactcttg 300
aacccgaagc ttgtttcact gaaggtaaag aaaagaatcc taatgttaat ctttcatttg 360
gagtgcagct tatttagctg ttggtcagct aanataaatc acatataata aaatngcact 420
ttgtaataga tataattcaa tcacctctaa tatnttgaca gacaaaaaaa cttaaagtct 480
agtgtcatgc tttgattata tctgcccaat atntgg 516

<210> 24
<211> 640
<212> DNA
<213> Homo sapiens

<400> 24
ccatttaaat gtggctgaat gtttccacaa cttcacacag ctgatgaatg tgctcttact 60
actctaggct tagagagcta tgctagcaag acagagatga gcatagtaat aaaaagacaa 120
gacaaggaca ttgctaaagg atattatgga agcagagaca ctttatctac ttttatttca 180
acactttctg caggctgtgt acaaagattc aagtgttgtc aaatcaatgt ggaagaaggc 240
agaggaaaac aatggtggaa cctgagaagg acgtgtttcc gaatagttga acataactgg 300
tttgagacct tcattgtttt catgattctc cttagtagtg gtgctctggt gagtgagatt 360
aagaaaaggt gatacagcac taatttttag aacactctaa tactgatgac ttattaatcc 420
tttgtttcat tgtcttagta tccaatgcat ttttaattat cccaccttgt atcttctata 480
gatttactct ataactctat atttctggat taacttttac tatgtatgta aatataattt 540
taagaagcta atcattaatt tttgcttact attaaatagc ccagaaagtg tagcccttca 600
gcttattcat taacaccaaa ggatgtgaat attcaattac 640

<210> 25
<211> 607

<212> DNA
<213> Homo sapiens

<400> 25
ccacatcagg atacaacatc aagaactatt tcctgactaa gtcaaattaa ttcattggaa 60
tcatactttt ctttttcttc caccaatagt ctttcccctg attaaataag taaaagacct 120
ttgcgaggaa aaaaaaaaag taacagtaac tactgtttct ctgccctcct attccaatga 180
aatgtcatat gcatatgatt aatttttttaa atagcttatg gagtataatt atttttgaaa 240
gctaataatg tgtaacattt tctttatagg catttgaaga tatatatatt gaycagcgaa 300
agacgattaa gacgatgttg gaatatgctg acaaggtttt cacttacatt ttcattctgg 360
aaatgcttct aaaatgggtg gcatatggct atcaaacata tttcaccaat gcctggagtt 420
ggctggactt cttaattgtt gatgtaggta tcgttcatat ttttgtctct gttcaaggta 480
gcttgtctta tttatattca aattctacaa tagtgagtct cagaccacta tgttatgttg 540
acagactata atarccacta aacgcatata tgcaatgaga gtgtcatttc tggaagacaa 600
gggctaa 607

<210> 26
<211> 336
<212> DNA
<213> Homo sapiens

<400> 26
aaaaattata cttgtcgtat tatatagcaa ctacacattg aatgatgatt ctgtttatta 60
attgttatta ttcytgtgtg tgcaggtttc attggtcagt ttaacagcaa atgccttggg 120
ttactcagaa cttggagcct atcaatctct caggacacta agagctctga gacctctaag 180
agccttatct cgatttgaag ggatgagggt aagaaaaatg aaagaacctg aagtattgta 240
tatagccaaa attaaactaa attaaattta gaaaaaagga aaaatgtatg catgcaaaag 300
gaatggcaaa ttcttgcaaa atgctcttta ttgttt 336

<210> 27
<211> 677
<212> DNA
<213> Homo sapiens

<400> 27
cttggttata ttgcctatag ttgttttcct aagtgtattg cttaagaaaa aaaaatgaat 60
tttaagattt ttttgaacct tgcttttaca tatcctagaa taaatagcat tgatagaaaa 120
aaagaatgga aagaccagag attactaggg gaatttttt tctttattaa cagataagaa 180
ttctgacttt tctttttttc catttgtgta ttaggtggtt gtgaatgccc ttttaggagc 240
aattccatcc atcatgaatg tgcttctggt ttgtcttata ttctggctaa ttttcagcat 300
catgggcgta aatttgtttg ctggcaaatt ctaccactgt attaacacca caactggtga 360
caggtttgac atcgaagacg tgaataatca tactgattgc ctaaaactaa tagaaagaaa 420
tgagactgct cgatggaaaa atgtgaaagt aaactttgat aatgtaggat ttgggtatct 480
ctctttgctt caagttgtaa gtgaacacta ttttctctga atatttttat tgtttggaat 540
aataacaaaa taatgacata catctattat ttagttccta agaaaaagta tatatttctt 600
tctatttaaa aaatttcaat ttgttagtac aagtttatga gcccagatgg gtgaaaactt 660

tattacatgt aaggact 677

<210> 28
<211> 457
<212> DNA
<213> Homo sapiens

<400> 28
aatggccatt ttgttcaata tgtgttctag aaatgaaaag ccatactaaa atactgtctt 60
ggtccaaaat ctgtgtaaaa tttgttttga aatgtctttc aaaaatattc ccttttgaaa 120
attatatcag taagaatatt tattaaacat caggtctaaa ttatttttac tccaaagtaa 180
aacatgcatg tccttcttaa taggccacat tcaaaggatg gatggatata atgtatgcag 240
cagttgattc cagaaatgta agtattcctt gtattctaag tctttttaca atattgatca 300
ggtggtaaaa ttaatcgaat aaagcataaa cgaccaaatg aaatgattct atcttgattt 360
aaaatatttg ggaaaaagtg tgacaggtaa atattcaagc atagcaatgt ttatcagaaa 420
gatcttacta agataattca acacatgaat tattttg 457

<210> 29
<211> 379
<212> DNA
<213> Homo sapiens

<400> 29
cagaaaaaaa aaaaatgctg acatattagt aagaataatt ttntctattg ttatgaaaaa 60
gcaccagtga cgatttccag cactaaaatg tatggtaata ttttacaaaa tattccccct 120
tggtaggtgg aactccagcc taagtatgaa gaaagtctgt acatgtatct ttactttgtt 180
attttcatca tctttgggtc cttcttcacc ttgaacctgt ttattggtgt catcatagat 240
aatttcaacc agcagaaaaa gaagataagt atttctaata ttttctctcc cactgagata 300
gaaaaattat tccttggagt gttttctctg ccaaatgagt acttgaattt agaacaaatg 360
ggagtatata ttataactg 379

<210> 30
<211> 393
<212> DNA
<213> Homo sapiens

<400> 30
gtcattttga attatttagg gaattaaaat attatcatac ctaaagagta caatttttt 60
tacattttaa atcccagata taattatact aatcagttga attttgtatt tctttttta 120
gccatccatt ttctatttta acattgaaaa aaatgtacaa aaggacacag ttttaaccag 180
tttgattttt cttttctata ctttggaggt caagacatct ttatgacaga agaacagaag 240
aaatactata atgcaatgaa aaaattagga tcgaaaaaac cgcaaaagcc tatacctcga 300
ccaggagtaa gaagtatcaa atgatatggg ggaaaataca aaaacaaaaa ctgcatgctt 360
gtctcacaaa aaagaaaagt aagctaaaca ttt 393

<210> 31
<211> 539
<212> DNA
<213> Homo sapiens

<400> 31
ttttaacaat taattatgct ataaattcat tcttacaaaa atcatttgga atgactactt 60
tgcaagaaac tagaaagtca attaatgcag aaagtactta atgctaatgc acatgagaaa 120
aactcctttg ttgttaaaag catttctatt tctctacaga acaaatttca aggaatggtc 180
tttgacttcg taaccagaca agtttttgac ataagcatca tgattctcat ctgtcttaac 240
atggtcacaa tgatggtgga aacagatgac cagagtgaat atgtgactac cattttgtca 300
cgcatcaatc tggtgttcat tgtgctattt actggagagt gtgtactgaa actcatctct 360
ctacgccatt attattttac cattggatgg aatatttttg attttgtggt tgtcattctc 420
tccattgtag gtaagaaata tttaaagttc ttaaattcag ttaaataaaa gtgaaagctg 480
aaacaatcaa gattagattc aagatcatcc cagcaatcag agataatcac tgtaaatat 539

<210> 32
<211> 3403
<212> DNA
<213> Homo sapiens

<400> 32
agtatatatt atatatagtt gtcatattta atataactgg gttcaggact ctgaacctta 60
ccttggagct ttagaagaaa catatgttta ttttaacgca tgatttcttc actggttggt 120
attctcattg tttattcata ggtatgtttc ttgccgagct gatagaaaag tatttcgtgt 180
cccctaccct gttccgagtg atccgtcttg ctaggattgg ccgaatccta cgtctgatca 240
aaggagcaaa ggggatccgc acgctgctct ttgctttgat gatgtccctt cctgcgttgt 300
ttaacatcgg cctcctactc ttcctagtca tgttcatcta cgccatcttt gggatgtcca 360
actttgccta tgttaagagg gaagttggga tcgatgacat gttcaacttt gagacctttg 420
gcaacagcat gatctgccta ttccaaatta caacctctgc tggctgggat ggattgctag 480
cacccattct caacagtaag ccacccgact gtgaccctaa taaagttaac cctggaagct 540
cagttaaggg agactgtggg aacccatctg ttggaatttt ctttttgtc agttacatca 600
tcatatcctt cctggttgtg gtgaacatgt acatcgcggt catcctggag aacttcagtg 660
ttgctactga agaaagtgca gagcctctga gtgaggatga ctttgagatg ttctatgagg 720
tttgggagaa gtttgatccc gatgcaactc agttcatgga atttgaaaaa ttatctcagt 780
ttgcagtgcg cttgaaccgc ctctcaatct gccacaacca aacaaactcc agctcattgc 840
catggatttg cccatggtga gtggtgaccg gatccactgt cttgatatct tatttgcttt 900
tacaaagcgg gttctaggag agagtggaga gatggatgct ctacgaatac agatggaaga 960
gcgattcatg gcttccaatc cttccaaggt ctcctatcag ccaatcacta ctactttaaa 1020
acgaaaacaa gaggaagtat ctgctgtcat tattcagcgt gcttacagac gccacctttt 1080
aaagcgaact gtaaaacaag cttcctttac gtacaataaa aacaaaatca aaggtggggc 1140
taatcttctt ataaaagaag acatgataat tgacagaata aatgaaaact ctattacaga 1200
aaaaactgat ctgaccatgt ccactgcagc ttgtccacct tcctatgacc gggtgacaaa 1260
gccaattgtg gaaaaacatg agcaagaagg caaagatgaa aaagccaaag ggaaataaat 1320
gaaaataaat aaaaataatt gggtgacaaa ttgtttacag cctgtgaagg tgatgtattt 1380
ttatcaacag gactccttta ggaggtcaat gccaaactga ctgtttttac acaaatctcc 1440

ttaaggtcag tgcctacaat aagacagtga ccccttgtca gcaaactgtg actctgtgta 1500
aaggggagat gaccttgaca ggaggttact gttctcacta ccagctgaca ctgctgaaga 1560
taagatgcac aatggctagt cagactgtag ggaccagttt caaggggtgc aaacctgtga 1620
ttttggggtt gtttaacatg aaacacttta gtgtagtaat tgtatccact gtttgcattt 1680
caactgccac atttgtcaca ttttttatgga atctgttagt ggattcatct ttttgttaat 1740
ccatgtgttt attatatgtg actatttttg taaacgaagt ttctgttgag aaataggcta 1800
aggacctcta taacaggtat gccacctggg gggtatggca accacatggc cctcccagct 1860
acacaaagtc gtggtttgca tgagggcatg ctgcacttag agatcatgca tgagaaaaag 1920
tcacaagaaa aacaaattct taaatttcac catatttctg ggaggggtaa ttgggtgata 1980
agtggaggtg ctttgttgat cttgttttgc gaaatccagc ccctagacca agtagattat 2040
ttgtgggtag gccagtaaat cttagcaggt gcaaacttca ttcaaatgtt tggagtcata 2100
aatgttatgt ttctttttgt tgtattaaaa aaaaaacctg aatagtgaat attgcccctc 2160
accctccacc gccagaagac tgaattgacc aaaattactc tttataaatt tctgcttttt 2220
cctgcacttt gtttagccat cttcggctct cagcaaggtt gacactgtat atgttaatga 2280
aatgctattt attatgtaaa tagtcatttt accctgtggt gcacgtttga gcaaacaaat 2340
aatgacctaa gcacagtatt tattgcatca aatatgtacc acaagaaatg tagagtgcaa 2400
gctttacaca ggtaataaaa tgtattctgt accatttata gatagtttgg atgctatcaa 2460
tgcatgttta tattaccatg ctgctgtatc tggtttctct cactgctcag aatctcattt 2520
atgagaaacc atatgtcagt ggtaaagtca aggaaattgt tcaacagatc tcatttattt 2580
aagtcattaa gcaatagttt gcagcacttt aacagctttt tggttatttt tacattttaa 2640
gtggataaca tatggtatat agccagactg tacagacatg tttaaaaaaa cacactgctt 2700
aacctattaa atatgtgttt agaattttat aagcaaatat aaatactgta aaaagtcact 2760
ttattttatt tttcagcatt atgtacataa atatgaagag gaaattatct tcaggttgat 2820
atcacaatca cttttcttac tttctgtcca tagtactttt tcatgaaaga aatttgctaa 2880
ataagacatg aaaacaagac tgggtagttg tagatttctg ctttttaaat tacatttgct 2940
aattttagat tatttcacaa ttttaaggag caaaataggt tcacgattca tatccaaatt 3000
atgctttgca attggaaaag ggtttaaaat tttatttata tttctggtag tacctgcact 3060
aactgaattg aaggtagtgc ttatgttatt tttgttcttt ttttctgact tcggtttatg 3120
ttttcatttc tttggagtaa tgctgctcta gattgttcta aatagaatgt gggcttcata 3180
attttttttt ccacaaaaac agagtagtca acttatatag tcaattacat caggacattt 3240
tgtgtttctt acagaagcaa accataggct cctcttttcc ttaaaactac ttagataaac 3300
tgtattcgtg aactgcatgc tggaaaatgc tactattatg ctaaataatg ctaaccaaca 3360
tttaaaatgt gcaaaactaa taaagattac atttttttatt tta 3403

<210> 33
<211> 8349
<212> DNA
<213> Homo sapiens

<400> 33
ttcttggtgc cagcttatca atcccaaact ctgggtgtaa aagattctac agggcacttt 60
cttatgcaag gagctaaaca gtgattaaag gagcaggatg aaaagatggc acagtcagtg 120
ctggtaccgc caggacctga cagcttccgc ttctttacca gggaatccct tgctgctatt 180
gaacaacgca ttgcagaaga gaaagctaag agacccaaac aggaacgcaa ggatgaggat 240
gatgaaaatg gcccaaagcc aaacagtgac ttggaagcag gaaaatctct tccatttatt 300
tatggagaca ttcctccaga gatggtgtca gtgcccctgg aggatctgga cccctactat 360
atcaataaga aaacgtttat agtattgaat aaagggaaag caatctctcg attcagtgcc 420

acccctgccc tttacatttt aactcccttc aaccctatta gaaaattagc tattaagatt 480
ttggtacatt ctttattcaa tatgctcatt atgtgcacga ttcttaccaa ctgtgtattt 540
atgaccatga gtaaccctcc agactggaca aagaatgtgg agtatacctt tacaggaatt 600
tatacttttg aatcacttat taaaatactt gcaaggggct tttgtttaga agatttcaca 660
tttttacggg atccatggaa ttggttggat ttcacagtca ttacttttgc atatgtgaca 720
gagtttgtgg acctgggcaa tgtctcagcg ttgagaacat tcagagttct ccgagcattg 780
aaaacaattt cagtcattcc aggcctgaag accattgtgg gggccctgat ccagtcagtg 840
aagaagcttt ctgatgtcat gatcttgact gtgttctgtc taagcgtgtt tgcgctaata 900
ggattgcagt tgttcatggg caacctacga aataaatgtt tgcaatggcc tccagataat 960
tcttcctttg aaataaatat cacttccttc tttaacaatt cattggatgg gaatggtact 1020
actttcaata ggacagtgag catatttaac tgggatgaat atattgagga taaaagtcac 1080
ttttatttt tagaggggca aaatgatgct ctgctttgtg gcaacagctc agatgcaggc 1140
cagtgtcctg aaggatacat ctgtgtgaag gctggtagaa accccaacta tggctacacg 1200
agctttgaca cctttagttg ggccttttg tccttatttc gtctcatgac tcaagacttc 1260
tgggaaaacc tttatcaact gacactacgt gctgctggga aaacgtacat gatatttttt 1320
gtgctggtca ttttcttggg ctcattctat ctaataaatt tgatcttggc tgtggtggcc 1380
atggcctatg aggaacagaa tcaggccaca ttggaagagg ctgaacagaa ggaagctgaa 1440
tttcagcaga tgctcgaaca gttgaaaaag caacaagaag aagctcaggc ggcagctgca 1500
gccgcatctg ctgaatcaag agacttcagt ggtgctggtg ggataggagt tttttcagag 1560
agttcttcag tagcatctaa gttgagctcc aaaagtgaaa aagagctgaa aaacagaaga 1620
aagaaaaaga aacagaaaga acagtctgga gaagaagaga aaaatgacag agtcctaaaa 1680
tcggaatctg aagacagcat aagaagaaaa ggtttccgtt tttccttgga aggaagtagg 1740
ctgacatatg aaaagagatt ttcttctcca caccagtcct tactgagcat ccgtggctcc 1800
cttttctctc caagacgcaa cagtagggcg agccttttca gcttcagagg tcgagcaaag 1860
gacattggct ctgagaatga ctttgctgat gatgagcaca gcacctttga ggacaatgac 1920
agccgaagag actctctgtt cgtgccgcac agacatggag aacggcgcca cagcaatgtc 1980
agccaggcca gccgtgcctc cagggtgctc cccatcctgc ccatgaatgg gaagatgcat 2040
agcgctgtgg actgcaatgg tgtggtctcc ctggtcgggg gcccttctac cctcacatct 2100
gctgggcagc tcctaccaga gggcacaact actgaaacag aaataagaaa gagacggtcc 2160
agttcttatc atgtttccat ggatttattg gaagatccta catcaaggca aagagcaatg 2220
agtatagcca gtattttgac caacaccatg gaagaacttg aagaatccag acagaaatgc 2280
ccaccatgct ggtataaatt tgctaatatg tgtttgattt gggactgttg taaaccatgg 2340
ttaaaggtga aacaccttgt caacctggtt gtaatggacc catttgttga cctggccatc 2400
accatctgca ttgtcttaaa tacactcttc atggctatgg agcactatcc catgacggag 2460
cagttcagca gtgtactgtc tgttggaaac ctggtcttca cagggatctt cacagcagaa 2520
atgtttctca agataattgc catggatcca tattattact ttcaagaagg ctggaatatt 2580
tttgatggtt ttattgtgag ccttagttta atggaacttg gtttggcaaa tgtggaagga 2640
ttgtcagttc tccgatcatt ccggctgctc cgagttttca agttggcaaa atcttggcca 2700
actctaaata tgctaattaa gatcattggc aattctgtgg gggctctagg aaacctcacc 2760
ttggtattgg ccatcatcgt cttcattttt gctgtggtcg gcatgcagct ctttggtaag 2820
agctacaaag aatgtgtctg caagatttcc aatgattgtg aactcccacg ctggcacatg 2880
catgactttt tccactcctt cctgatcgtg ttccgcgtgc tgtgtggaga gtggatagag 2940
accatgtggg actgtatgga ggtcgctggc caaaccatgt gccttactgt cttcatgatg 3000
gtcatggtga ttggaaatct agtggttctg aacctcttct tggccttgct tttgagttcc 3060
ttcagttctg acaatcttgc tgccactgat gatgataacg aaatgaataa tctccagatt 3120
gctgtgggaa ggatgcagaa aggaatcgat tttgttaaaa gaaaaatacg tgaatttatt 3180
cagaaagcct ttgttaggaa gcagaaagct ttagatgaaa ttaaaccgct tgaagatcta 3240
aataataaaa aagacagctg tatttccaac cataccacca tagaaatagg caaagacctc 3300

aattatctca aagacggaaa tggaactact agtggcatag gcagcagtgt agaaaaatat 3360
gtcgtggatg aaagtgatta catgtcattt ataaacaacc ctagcctcac tgtgacagta 3420
ccaattgctg ttggagaatc tgactttgaa aatttaaata ctgaagaatt cagcagcgag 3480
tcagatatgg aggaaagcaa agagaagcta aatgcaacta gttcatctga aggcagcacg 3540
gttgatattg gagctcccgc cgagggagaa cagcctgagg ttgaacctga ggaatccctt 3600
gaacctgaag cctgttttac agaagactgt gtacggaagt tcaagtgttg tcagataagc 3660
atagaagaag gcaaagggaa actctggtgg aatttgagga aaacatgcta taagatagtg 3720
gagcacaatt ggttcgaaac cttcattgtc ttcatgattc tgctgagcag tggggctctg 3780
gcctttgaag atatatacat tgagcagcga aaaaccatta agaccatgtt agaatatgct 3840
gacaaggttt tcacttacat attcattctg gaaatgctgc taaagtgggt tgcatatggt 3900
tttcaagtgt attttaccaa tgcctggtgc tggctagact tcctgattgt tgatgtctca 3960
ctggttagct taactgcaaa tgccttgggt tactcagaac ttggtgccat caaatccctc 4020
agaacactaa gagctctgag gccactgaga gctttgtccc ggtttgaagg aatgagggct 4080
gttgtaaatg ctcttttagg agccattcca tctatcatga atgtacttct ggtttgtctg 4140
atcttttggc taatattcag tatcatggga gtgaatctct ttgctggcaa gttttaccat 4200
tgtattaatt acaccactgg agagatgttt gatgtaagcg tggtcaacaa ctacagtgag 4260
tgcaaagctc tcattgagag caatcaaact gccaggtgga aaaatgtgaa agtaaacttt 4320
gataacgtag gacttggata tctgtctcta cttcaagtag ccacgtttaa gggatggatg 4380
gatattatgt atgcagctgt tgattcacga aatgtagaat tacaacccaa gtatgaagac 4440
aacctgtaca tgtatcttta ttttgtcatc tttattattt ttggttcatt ctttaccttg 4500
aatcttttca ttggtgtcat catagataac ttcaaccaac agaaaaagaa gtttggaggt 4560
caagacattt ttatgacaga agaacagaag aaatactaca atgcaatgaa aaaactgggt 4620
tcaaagaaac cacaaaaacc catacctcga cctgctaaca aattccaagg aatggtcttt 4680
gattttgtaa ccaaacaagt ctttgatatc agcatcatga tcctcatctg ccttaacatg 4740
gtcaccatga tggtggaaac cgatgaccag agtcaagaaa tgacaaacat tctgtactgg 4800
attaatctgg tgtttattgt tctgttcact ggagaatgtg tgctgaaact gatctctctt 4860
cgttactact atttcactat tggatggaat atttttgatt ttgtggtggt cattctctcc 4920
attgtaggaa tgtttctggc tgaactgata gaaaagtatt ttgtgtcccc taccctgttc 4980
cgagtgatcc gtcttgccag gattggccga atcctacgtc tgatcaaagg agcaaagggg 5040
atccgcacgc tgctctttgc tttgatgatg tcccttcctg cgttgtttaa catcggcctc 5100
cttcttttcc tggtcatgtt catctacgcc atctttggga tgtccaattt tgcctatgtt 5160
aagagggaag ttgggatcga tgacatgttc aactttgaga cctttggcaa cagcatgatc 5220
tgcctgttcc aaattacaac ctctgctggc tgggatggat tgctagcacc tattcttaat 5280
agtggacctc cagactgtga ccctgacaaa gatcaccctg gaagctcagt taaaggagac 5340
tgtgggaacc catctgttgg gatttttctt tttgtcagtt acatcatcat atccttcctg 5400
gttgtggtga acatgtacat cgcggtcatc ctggagaact tcagtgttgc tactgaagaa 5460
agtgcagagc ctctgagtga ggatgacttt gagatgttct atgaggtttg ggagaagttt 5520
gatcccgatg cgacccagtt tatagagttt gccaaacttt ctgattttgc agatgccctg 5580
gatcctcctc ttctcatagc aaaacccaac aaagtccagc tcattgccat ggatctgccc 5640
atggtgagtg gtgaccggat ccactgtctt gacatcttat ttgcttttac aaagcgtgtt 5700
ttgggtgaga gtggagagat ggatgccctt cgaatacaga tggaagagcg attcatggca 5760
tcaaacccct ccaaagtctc ttatgagccc attacgacca cgttgaaacg caaacaagag 5820
gaggtgtctg ctattattat ccagagggct tacagacgct acctcttgaa gcaaaaagtt 5880
aaaaaggtat caagtatata caagaaagac aaaggcaaag aatgtgatgg aacacccatc 5940
aaagaagata ctctcattga taaactgaat gagaattcaa ctccagagaa aaccgatatg 6000
acgccttcca ccacgtctcc accctcgtat gatagtgtga ccaaaccaga aaaagaaaaa 6060
tttgaaaaag acaaatcaga aaaggaagac aaagggaaag atatcaggga aagtaaaaag 6120
taaaaagaaa ccaagaattt tccattttgt gatcaattgt ttacagcccg tgatggtgat 6180

gtgtttgtgt caacaggact cccacaggag gtctatgcca aactgactgt ttttacaaat 6240
gtatacttaa ggtcagtgcc tataacaaga cagagacctc tggtcagcaa actggaactc 6300
agtaaactgg agaaatagta tcgatgggag gtttctattt tcacaaccag ctgacactgc 6360
tgaagagcag aggcgtaatg gctactcaga cgataggaac caatttaaag gggggaggga 6420
agttaaattt ttatgtaaat tcaacatgtg acacttgata atagtaattg tcaccagtgt 6480
ttatgtttta actgccacac ctgccatatt tttacaaaac gtgtgctgtg aatttatcac 6540
ttttcttttt aattcacagg ttgtttacta ttatatgtga ctatttttgt aaatgggttt 6600
gtgtttgggg agagggatta aagggaggga attctacatt tctctattgt attgtataac 6660
tggatatatt ttaaatggag gcatgctgca attctcattc acacataaaa aaatcacatc 6720
acaaaaggga agagtttact tcttgtttca ggatgttttt agatttttga ggtgcttaaa 6780
tagctattcg tatttttaag gtgtctcatc cagaaaaaat ttaatgtgcc tgtaaatgtt 6840
ccatagaatc acaagcatta aagagttgtt ttatttttac ataacccatt aaatgtacat 6900
gtatatatgt atatatgtat atgtgcgtgt atatacatat atatgtatac acacatgcac 6960
acacagagat atacacatac cattacattg tcattcacag tcccagcagc atgactatca 7020
cattttgat aagtgtcctt tggcataaaa taaaaatatc ctatcagtcc tttctaagaa 7080
gcctgaattg accaaaaaac atccccacca ccactttata aagttgattc tgctttatcc 7140
tgcagtattg tttagccatc ttctgctctt ggtaaggttg acatagtata tgtcaattta 7200
aaaaataaaa gtctgctttg taaatagtaa ttttacccag tggtgcatgt ttgagcaaac 7260
aaaaatgatg atttaagcac actacttatt gcatcaaata tgtaccacag taagtatagt 7320
ttgcaagctt tcaacaggta atatgatgta attggttcca ttatagtttg aagctgtcac 7380
tgctgcatgt ttatcttgcc tatgctgctg tatcttattc cttccactgt tcagaagtct 7440
aatatgggaa gccatatatc agtggtaaag tgaagcaaat tgttctacca agacctcatt 7500
cttcatgtca ttaagcaata ggttgcagca aacaaggaag agcttcttgc tttttattct 7560
tccaacctta attgaacact caatgatgaa aagcccgact gtacaaacat gttgcaagct 7620
gcttaaatct gtttaaaata tatggttaga gttttctaag aaaatataaa tactgtaaaa 7680
agttcatttt attttatttt tcagcctttt gtacgtaaaa tgagaaatta aaagtatctt 7740
caggtggatg tcacagtcac tattgttagt ttctgttcct agcactttta aattgaagca 7800
cttcacaaaa taagaagcaa ggactaggat gcagtgtagg tttctgcttt tttattagta 7860
ctgtaaactt gcacacattt caatgtgaaa caaatctcaa actgagttca atgtttattt 7920
gctttcaata gtaatgcctt atcattgaaa gaggcttaaa gaaaaaaaaa atcagctgat 7980
actcttggca ttgcttgaat ccaatgtttc cacctagtct ttttattcag taatcatcag 8040
tcttttccaa tgtttgttta cacagataga tcttattgac ccatatggca ctagaactgt 8100
atcagatata atatgggatc ccagcttttt ttcctctccc acaaaaccag gtagtgaagt 8160
tatattacca gttacagcaa aatactttgt gtttcacaag caacaataaa tgtagattct 8220
ttatactgaa gctattgact tgtagtgtgt tggtgaatgc atgcaggaag atgctgttac 8280
cataaagaac ggtaaaccac attacaatca agccaaagaa taaaggttcg cttatgtata 8340
tgtatttaa 8349

<210> 34
<211> 8349
<212> DNA
<213> Homo sapiens

<400> 34
ttcttggtgc cagcttatca atcccaaact ctgggtgtaa aagattctac agggcacttt 60
cttatgcaag gagctaaaca gtgattaaag gagcaggatg aaaagatggc acagtcagtg 120
ctggtaccgc caggacctga cagcttccgc ttctttacca gggaatccct tgctgctatt 180

gaacaacgca ttgcagaaga gaaagctaag agacccaaac aggaacgcaa ggatgaggat 240
gatgaaaatg gcccaaagcc aaacagtgac ttggaagcag gaaaatctct tccatttatt 300
tatggagaca ttcctccaga gatggtgtca gtgcccctgg aggatctgga cccctactat 360
atcaataaga aaacgtttat agtattgaat aaagggaaag caatctctcg attcagtgcc 420
acccctgccc tttacatttt aactcccttc aaccctatta gaaaattagc tattaagatt 480
ttggtacatt ctttattcaa tatgctcatt atgtgcacga ttcttaccaa ctgtgtattt 540
atgaccatga gtaaccctcc agactggaca aagaatgtgg agtatacctt tacaggaatt 600
tatacttttg aatcacttat taaaatactt gcaaggggct tttgtttaga agatttcaca 660
tttttacggg atccatggaa ttggttggat ttcacagtca ttacttttgc atatgtgaca 720
gagtttgtgg acctgggcaa tgtctcagcg ttgagaacat tcagagttct ccgagcattg 780
aaaacaattt cagtcattcc aggcctgaag accattgtgg gggccctgat ccagtcagtg 840
aagaagcttt ctgatgtcat gatcttgact gtgttctgtc taagcgtgtt tgcgctaata 900
ggattgcagt tgttcatggg caacctacga aataaatgtt tgcaatggcc tccagataat 960
tcttcctttg aaataaatat cacttccttc tttaacaatt cattggatgg gaatggtact 1020
actttcaata ggacagtgag catatttaac tgggatgaat atattgagga taaaagtcac 1080
ttttatttt tagaggggca aaatgatgct ctgctttgtg gcaacagctc agatgcaggc 1140
cagtgtcctg aaggatacat ctgtgtgaag gctggtagaa accccaacta tggctacacg 1200
agctttgaca cctttagttg ggccttttg tccttatttc gtctcatgac tcaagacttc 1260
tgggaaaacc tttatcaact gacactacgt gctgctggga aaacgtacat gatatttttt 1320
gtgctggtca ttttcttggg ctcattctat ctaataaatt tgatcttggc tgtggtggcc 1380
atggcctatg aggaacagaa tcaggccaca ttggaagagg ctgaacagaa ggaagctgaa 1440
tttcagcaga tgctcgaaca gttgaaaaag caacaagaag aagctcaggc ggcagctgca 1500
gccgcatctg ctgaatcaag agacttcagt ggtgctggtg ggataggagt tttttcagag 1560
agttcttcag tagcatctaa gttgagctcc aaaagtgaaa aagagctgaa aaacagaaga 1620
aagaaaaaga aacagaaaga acagtctgga gaagaagaga aaaatgacag agtcctaaaa 1680
tcggaatctg aagacagcat aagaagaaaa ggtttccgtt tttccttgga aggaagtagg 1740
ctgacatatg aaaagagatt ttcttctcca caccagtcct tactgagcat ccgtggctcc 1800
cttttctctc caagacgcaa cagtagggcg agccttttca gcttcagagg tcgagcaaag 1860
gacattggct ctgagaatga ctttgctgat gatgagcaca gcacctttga ggacaatgac 1920
agccgaagag actctctgtt cgtgccgcac agacatggag aacggcgcca cagcaatgtc 1980
agccaggcca gccgtgcctc cagggtgctc cccatcctgc ccatgaatgg gaagatgcat 2040
agcgctgtgg actgcaatgg tgtggtctcc ctggtcgggg gcccttctac cctcacatct 2100
gctgggcagc tcctaccaga gggcacaact actgaaacag aaataagaaa gagacggtcc 2160
agttcttatc atgtttccat ggatttattg gaagatccta catcaaggca aagagcaatg 2220
agtatagcca gtattttgac caacaccatg gaagaacttg aagaatccag acagaaatgc 2280
ccaccatgct ggtataaatt tgctaatatg tgtttgattt gggactgttg taaaccatgg 2340
ttaaaggtga aacaccttgt caacctggtt gtaatggacc catttgttga cctggccatc 2400
accatctgca ttgtcttaaa tacactcttc atggctatgg agcactatcc catgacggag 2460
cagttcagca gtgtactgtc tgttggaaac ctggtcttca cagggatctt cacagcagaa 2520
atgtttctca agataattgc catggatcca tattattact ttcaagaagg ctggaatatt 2580
tttgatggtt ttattgtgag ccttagttta atggaacttg gtttggcaaa tgtggaagga 2640
ttgtcagttc tccgatcatt ccggctgctc cgagttttca agttggcaaa atcttggcca 2700
actctaaata tgctaattaa gatcattggc aattctgtgg gggctctagg aaacctcacc 2760
ttggtattgg ccatcatcgt cttcattttt gctgtggtcg gcatgcagct ctttggtaag 2820
agctacaaag aatgtgtctg caagatttcc aatgattgtg aactcccacg ctggcacatg 2880
catgactttt tccactcctt cctgatcgtg ttccgcgtgc tgtgtggaga gtggatagag 2940
accatgtggg actgtatgga ggtcgctggc caaaccatgt gccttactgt cttcatgatg 3000
gtcatggtga ttggaaatct agtggttctg aacctcttct tggccttgct tttgagttcc 3060

ttcagttctg acaatcttgc tgccactgat gatgataacg aaatgaataa tctccagatt 3120
gctgtgggaa ggatgcagaa aggaatcgat tttgttaaaa gaaaaatacg tgaatttatt 3180
cagaaagcct ttgttaggaa gcagaaagct ttagatgaaa ttaaaccgct tgaagatcta 3240
aataataaaa aagacagctg tatttccaac cataccacca tagaaatagg caaagacctc 3300
aattatctca aagacggaaa tggaactact agtggcatag gcagcagtgt agaaaaatat 3360
gtcgtggatg aaagtgatta catgtcattt ataaacaacc ctagcctcac tgtgacagta 3420
ccaattgctg ttggagaatc tgactttgaa aatttaaata ctgaagaatt cagcagcgag 3480
tcagatatgg aggaaagcaa agagaagcta aatgcaacta gttcatctga aggcagcacg 3540
gttgatattg gagctcccgc cgagggagaa cagcctgagg ttgaacctga ggaatccctt 3600
gaacctgaag cctgttttac agaagactgt gtacggaagt tcaagtgttg tcagataagc 3660
atagaagaag gcaaagggaa actctggtgg aatttgagga aaacatgcta taagatagtg 3720
gagcacaatt ggttcgaaac cttcattgtc ttcatgattc tgctgagcag tggggctctg 3780
gcctttgaag atatatacat tgagcagcga aaaaccatta agaccatgtt agaatatgct 3840
gacaaggttt tcacttacat attcattctg gaaatgctgc taaagtgggt tgcatatggt 3900
tttcaagtgt attttaccaa tgcctggtgc tggctagact tcctgattgt tgatgtctca 3960
ctggttagct taactgcaaa tgccttgggt tactcagaac ttggtgccat caaatccctc 4020
agaacactaa gagctctgag gccactgaga gctttgtccc ggtttgaagg aatgagggct 4080
gttgtaaatg ctcttttagg agccattcca tctatcatga atgtacttct ggtttgtctg 4140
atcttttggc taatattcag tatcatggga gtgaatctct ttgctggcaa gttttaccat 4200
tgtattaatt acaccactgg agagatgttt gatgtaagcg tggtcaacaa ctacagtgag 4260
tgcaaagctc tcattgagag caatcaaact gccaggtgga aaaatgtgaa agtaaacttt 4320
gataacgtag gacttggata tctgtctcta cttcaagtag ccacgtttaa gggatggatg 4380
gatattatgt atgcagctgt tgattcacga aatgtagaat tacaacccaa gtatgaagac 4440
aacctgtaca tgtatcttta ttttgtcatc tttattattt ttggttcatt ctttaccttg 4500
aatcttttca ttggtgtcat catagataac ttcaaccaac agaaaaagaa gtttggaggt 4560
caagacattt ttatgacaga agaacagaag aaatactaca atgcaatgaa aaaactgggt 4620
tcaaagaaac cacaaaaacc catacctcga cctgctaaca aattccaagg aatggtcttt 4680
gattttgtaa ccaaacaagt ctttgatatc agcatcatga tcctcatctg ccttaacatg 4740
gtcaccatga tggtggaaac cgatgaccag agtcaagaaa tgacaaacat tctgtactgg 4800
attaatctgg tgtttattgt tctgttcact ggagaatgtg tgctgaaact gatctctctt 4860
cgttactact atttcactat tggatggaat atttttgatt ttgtggtggt cattctctcc 4920
attgtaggaa tgtttctggc tgaactgata gaaaagtatt ttgtgtcccc taccctgttc 4980
cgagtgatcc gtcttgccag gattggccga atcctacgtc tgatcaaagg agcaaagggg 5040
atccgcacgc tgctctttgc tttgatgatg tcccttcctg cgttgtttaa catcggcctc 5100
cttcttttcc tggtcatgtt catctacgcc atctttggga tgtccaattt tgcctatgtt 5160
aagagggaag ttgggatcga tgacatgttc aactttgaga cctttggcaa cagcatgatc 5220
tgcctgttcc aaattacaac ctctgctggc tgggatggat tgctagcacc tattcttaat 5280
agtggacctc cagactgtga ccctgacaaa gatcaccctg gaagctcagt taaaggagac 5340
tgtgggaacc catctgttgg gattttcttt tttgtcagtt acatcatcat atccttcctg 5400
gttgtggtga acatgtacat cgcggtcatc ctggagaact tcagtgttgc tactgaagaa 5460
agtgcagagc ctctgagtga ggatgacttt gagatgttct atgaggtttg ggagaagttt 5520
gatcccgatg cgacccagtt tatagagttt gccaaacttt ctgattttgc agatgccctg 5580
gatcctcctc ttctcatagc aaaacccaac aaagtccagc tcattgccat ggatctgccc 5640
atggtgagtg gtgaccggat ccactgtctt gacatcttat ttgcttttac aaagcgtgtt 5700
ttgggtgaga gtggagagat ggatgccctt cgaatacaga tggaagagcg attcatggca 5760
tcaaacccct ccaaagtctc ttatgagccc attacgacca cgttgaaacg caaacaagag 5820
gaggtgtctg ctattattat ccagagggct tacagacgct acctcttgaa gcaaaaagtt 5880
aaaaaggtat caagtatata caagaaagac aaaggcaaag aatgtgatgg aacacccatc 5940

aaagaagata ctctcattga taaactgaat gagaattcaa ctccagagaa aaccgatatg 6000
acgccttcca ccacgtctcc accctcgtat gatagtgtga ccaaaccaga aaaagaaaaa 6060
tttgaaaaag acaaatcaga aaaggaagac aaagggaaag atatcaggga aagtaaaaag 6120
taaaaagaaa ccaagaattt tccattttgt gatcaattgt ttacagcccg tgatggtgat 6180
gtgtttgtgt caacaggact cccacaggag gtctatgcca aactgactgt ttttacaaat 6240
gtatacttaa ggtcagtgcc tataacaaga cagagacctc tggtcagcaa actggaactc 6300
agtaaactgg agaaatagta tcgatgggag gtttctattt tcacaaccag ctgacactgc 6360
tgaagagcag aggcgtaatg gctactcaga cgataggaac caatttaaag gggggaggga 6420
agttaaattt ttatgtaaat tcaacatgtg acacttgata atagtaattg tcaccagtgt 6480
ttatgtttta actgccacac ctgccatatt tttacaaaac gtgtgctgtg aatttatcac 6540
ttttcttttt aattcacagg ttgtttacta ttatatgtga ctatttttgt aaatgggttt 6600
gtgtttgggg agagggatta aagggaggga attctacatt tctctattgt attgtataac 6660
tggatatatt ttaaatggag gcatgctgca attctcattc acacataaaa aaatcacatc 6720
acaaaaggga agagtttact tcttgtttca ggatgttttt agatttttga ggtgcttaaa 6780
tagctattcg tatttttaag gtgtctcatc cagaaaaaat ttaatgtgcc tgtaaatgtt 6840
ccatagaatc acaagcatta aagagttgtt ttatttttac ataacccatt aaatgtacat 6900
gtatatatgt atatatgtat atgtgcgtgt atatacatat atatgtatac acacatgcac 6960
acacagagat atacacatac cattacattg tcattcacag tcccagcagc atgactatca 7020
catttttgat aagtgtcctt tggcataaaa taaaaatatc ctatcagtcc tttctaagaa 7080
gcctgaattg accaaaaaac atccccacca ccactttata aagttgattc tgctttatcc 7140
tgcagtattg tttagccatc ttctgctctt ggtaaggttg acatagtata tgtcaattta 7200
aaaaataaaa gtctgctttg taaatagtaa ttttacccag tggtgcatgt ttgagcaaac 7260
aaaaatgatg atttaagcac actacttatt gcatcaaata tgtaccacag taagtatagt 7320
ttgcaagctt tcaacaggta atatgatgta attggttcca ttatagtttg aagctgtcac 7380
tgctgcatgt ttatcttgcc tatgctgctg tatcttattc cttccactgt tcagaagtct 7440
aatatgggaa gccatatatc agtggtaaag tgaagcaaat tgttctacca agacctcatt 7500
cttcatgtca ttaagcaata ggttgcagca aacaaggaag agcttcttgc tttttattct 7560
tccaacctta attgaacact caatgatgaa aagcccgact gtacaaacat gttgcaagct 7620
gcttaaatct gtttaaaata tatggttaga gttttctaag aaaatataaa tactgtaaaa 7680
agttcatttt attttatttt tcagcctttt gtacgtaaaa tgagaaatta aaagtatctt 7740
caggtggatg tcacagtcac tattgttagt ttctgttcct agcactttta aattgaagca 7800
cttcacaaaa taagaagcaa ggactaggat gcagtgtagg tttctgcttt tttattagta 7860
ctgtaaactt gcacacattt caatgtgaaa caaatctcaa actgagttca atgtttattt 7920
gctttcaata gtaatgcctt atcattgaaa gaggcttaaa gaaaaaaaaa atcagctgat 7980
actcttggca ttgcttgaat ccaatgtttc cacctagtct ttttattcag taatcatcag 8040
tcttttccaa tgtttgttta cacagataga tcttattgac ccatatggca ctagaactgt 8100
atcagatata atatgggatc ccagcttttt ttcctctccc acaaaaccag gtagtgaagt 8160
tatattacca gttacagcaa aatactttgt gtttcacaag caacaataaa tgtagattct 8220
ttatactgaa gctattgact tgtagtgtgt tggtgaatgc atgcaggaag atgctgttac 8280
cataaagaac ggtaaaccac attacaatca agccaaagaa taaaggttcg cttatgtata 8340
tgtatttaa 8349

<210> 35
<211> 2005
<212> PRT
<213> Homo sapiens

<400> 35

```
Met Ala Gln Ser Val Leu Val Pro Pro Gly Pro Asp Ser Phe Arg Phe
 1               5                  10                  15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Gln Arg Ile Ala Glu Glu
            20                  25                  30

Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn
        35                  40                  45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe
    50                  55                  60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp
65                  70                  75                  80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys
                85                  90                  95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu
            100                 105                 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
        115                 120                 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val
    130                 135                 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr
145                 150                 155                 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala
                165                 170                 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn
            180                 185                 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val
        195                 200                 205

Asp Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala
    210                 215                 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala
225                 230                 235                 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val
                245                 250                 255
```

Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly
260 265 270

Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe
275 280 285

Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly
290 295 300

Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile
305 310 315 320

Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu
325 330 335

Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile
340 345 350

Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp
355 360 365

Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp
370 375 380

Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr
385 390 395 400

Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu
405 410 415

Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn
420 425 430

Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln
435 440 445

Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala
450 455 460

Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile
465 470 475 480

Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys
485 490 495

Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Lys Gln Lys Glu
500 505 510

```
Gln Ser Gly Glu Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser
        515                 520                 525

Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser
    530                 535                 540

Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu
545                 550                 555                 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser
                565                 570                 575

Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp
            580                 585                 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg
        595                 600                 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn
    610                 615                 620

Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met
625                 630                 635                 640

Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu
                645                 650                 655

Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu
            660                 665                 670

Gly Thr Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Ser Tyr
        675                 680                 685

His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala
    690                 695                 700

Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
705                 710                 715                 720

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys
                725                 730                 735

Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val
            740                 745                 750

Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
        755                 760                 765
```

```
Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
    770                 775                 780

Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly
785                 790                 795                 800

Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr
                805                 810                 815

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser
            820                 825                 830

Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val
        835                 840                 845

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
    850                 855                 860

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
865                 870                 875                 880

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
                885                 890                 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
            900                 905                 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe
        915                 920                 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
    930                 935                 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
945                 950                 955                 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn
                965                 970                 975

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
            980                 985                 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
        995                 1000                1005

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu Phe
   1010                1015                1020
```

Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu Ile Lys
1025 1030 1035 1040

Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile Ser Asn His
1045 1050 1055

Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn
1060 1065 1070

Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp
1075 1080 1085

Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr
1090 1095 1100

Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu
1105 1110 1115 1120

Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn
1125 1130 1135

Ala Thr Ser Ser Ser Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Ala
1140 1145 1150

Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu
1155 1160 1165

Ala Cys Phe Thr Glu Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile
1170 1175 1180

Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr
1185 1190 1195 1200

Cys Tyr Lys Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe
1205 1210 1215

Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile
1220 1225 1230

Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val
1235 1240 1245

Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr
1250 1255 1260

Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu
1265 1270 1275 1280

Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr
1285 1290 1295

Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg
1300 1305 1310

Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Ala Val Val Asn
1315 1320 1325

Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys
1330 1335 1340

Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala
1345 1350 1355 1360

Gly Lys Phe Tyr His Cys Ile Asn Tyr Thr Thr Gly Glu Met Phe Asp
1365 1370 1375

Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser
1380 1385 1390

Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val
1395 1400 1405

Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp
1410 1415 1420

Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln
1425 1430 1435 1440

Pro Lys Tyr Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe
1445 1450 1455

Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile
1460 1465 1470

Ile Asp Asn Phe Asn Gln Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile
1475 1480 1485

Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu
1490 1495 1500

Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe
1505 1510 1515 1520

Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser
1525 1530 1535

Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr
1540 1545 1550

Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu
1555 1560 1565

Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser
1570 1575 1580

Leu Arg Tyr Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val
1585 1590 1595 1600

Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu Leu Ile Glu
1605 1610 1615

Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg
1620 1625 1630

Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr
1635 1640 1645

Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly
1650 1655 1660

Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser
1665 1670 1675 1680

Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn
1685 1690 1695

Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr
1700 1705 1710

Ser Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro
1715 1720 1725

Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys Gly
1730 1735 1740

Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile
1745 1750 1755 1760

Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu
1765 1770 1775

Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu
1780 1785 1790

Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp
1795 1800 1805

Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala
1810 1815 1820

Leu Asp Pro Pro Leu Leu Ile Ala Lys Pro Asn Lys Val Gln Leu Ile
1825 1830 1835 1840

Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp
1845 1850 1855

Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met
1860 1865 1870

Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro
1875 1880 1885

Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln
1890 1895 1900

Glu Glu Val Ser Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu
1905 1910 1915 1920

Leu Lys Gln Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys
1925 1930 1935

Gly Lys Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp
1940 1945 1950

Lys Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser
1955 1960 1965

Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys Glu
1970 1975 1980

Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys Asp Ile
1985 1990 1995 2000

Arg Glu Ser Lys Lys
2005

<210> 36
<211> 2005
<212> PRT
<213> Homo sapiens

<400> 36

```
Met Ala Gln Ser Val Leu Val Pro Pro Gly Pro Asp Ser Phe Arg Phe
 1               5                  10                  15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Gln Arg Ile Ala Glu Glu
            20                  25                  30

Lys Ala Lys Arg Pro Lys Gln Glu Arg Lys Asp Glu Asp Asp Glu Asn
        35                  40                  45

Gly Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Ser Leu Pro Phe
    50                  55                  60

Ile Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Val Pro Leu Glu Asp
65                  70                  75                  80

Leu Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Leu Asn Lys
                85                  90                  95

Gly Lys Ala Ile Ser Arg Phe Ser Ala Thr Pro Ala Leu Tyr Ile Leu
            100                 105                 110

Thr Pro Phe Asn Pro Ile Arg Lys Leu Ala Ile Lys Ile Leu Val His
        115                 120                 125

Ser Leu Phe Asn Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val
    130                 135                 140

Phe Met Thr Met Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr
145                 150                 155                 160

Thr Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala
                165                 170                 175

Arg Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn
            180                 185                 190

Trp Leu Asp Phe Thr Val Ile Thr Phe Ala Tyr Val Thr Glu Phe Val
        195                 200                 205

Asn Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala
    210                 215                 220

Leu Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala
225                 230                 235                 240

Leu Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val
```

245 250 255

Phe Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly
260 265 270

Asn Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Asp Asn Ser Ser Phe
275 280 285

Glu Ile Asn Ile Thr Ser Phe Phe Asn Asn Ser Leu Asp Gly Asn Gly
290 295 300

Thr Thr Phe Asn Arg Thr Val Ser Ile Phe Asn Trp Asp Glu Tyr Ile
305 310 315 320

Glu Asp Lys Ser His Phe Tyr Phe Leu Glu Gly Gln Asn Asp Ala Leu
325 330 335

Leu Cys Gly Asn Ser Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile
340 345 350

Cys Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp
355 360 365

Thr Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp
370 375 380

Phe Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr
385 390 395 400

Tyr Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu
405 410 415

Ile Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Glu Gln Asn
420 425 430

Gln Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln
435 440 445

Met Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Ala Ala
450 455 460

Ala Ala Ala Ser Ala Glu Ser Arg Asp Phe Ser Gly Ala Gly Gly Ile
465 470 475 480

Gly Val Phe Ser Glu Ser Ser Ser Val Ala Ser Lys Leu Ser Ser Lys
485 490 495

Ser Glu Lys Glu Leu Lys Asn Arg Arg Lys Lys Lys Lys Gln Lys Glu

500 505 510

Gln Ser Gly Glu Glu Glu Lys Asn Asp Arg Val Leu Lys Ser Glu Ser
515 520 525

Glu Asp Ser Ile Arg Arg Lys Gly Phe Arg Phe Ser Leu Glu Gly Ser
530 535 540

Arg Leu Thr Tyr Glu Lys Arg Phe Ser Ser Pro His Gln Ser Leu Leu
545 550 555 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Arg Ala Ser
565 570 575

Leu Phe Ser Phe Arg Gly Arg Ala Lys Asp Ile Gly Ser Glu Asn Asp
580 585 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Asn Asp Ser Arg Arg
595 600 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg His Ser Asn
610 615 620

Val Ser Gln Ala Ser Arg Ala Ser Arg Val Leu Pro Ile Leu Pro Met
625 630 635 640

Asn Gly Lys Met His Ser Ala Val Asp Cys Asn Gly Val Val Ser Leu
645 650 655

Val Gly Gly Pro Ser Thr Leu Thr Ser Ala Gly Gln Leu Leu Pro Glu
660 665 670

Gly Thr Thr Thr Glu Thr Glu Ile Arg Lys Arg Arg Ser Ser Ser Tyr
675 680 685

His Val Ser Met Asp Leu Leu Glu Asp Pro Thr Ser Arg Gln Arg Ala
690 695 700

Met Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
705 710 715 720

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Lys Phe Ala Asn Met Cys
725 730 735

Leu Ile Trp Asp Cys Cys Lys Pro Trp Leu Lys Val Lys His Leu Val
740 745 750

Asn Leu Val Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys

```
        755                 760                 765

Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
    770                 775                 780

Glu Gln Phe Ser Ser Val Leu Ser Val Gly Asn Leu Val Phe Thr Gly
785                 790                 795                 800

Ile Phe Thr Ala Glu Met Phe Leu Lys Ile Ile Ala Met Asp Pro Tyr
                805                 810                 815

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Phe Ile Val Ser
            820                 825                 830

Leu Ser Leu Met Glu Leu Gly Leu Ala Asn Val Glu Gly Leu Ser Val
        835                 840                 845

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
    850                 855                 860

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
865                 870                 875                 880

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
                885                 890                 895

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
            900                 905                 910

Lys Ile Ser Asn Asp Cys Glu Leu Pro Arg Trp His Met His Asp Phe
        915                 920                 925

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
    930                 935                 940

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
945                 950                 955                 960

Thr Val Phe Met Met Val Met Val Ile Gly Asn Leu Val Val Leu Asn
                965                 970                 975

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
            980                 985                 990

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
        995                1000                1005

Arg Met Gln Lys Gly Ile Asp Phe Val Lys Arg Lys Ile Arg Glu Phe
```

1010 1015 1020

Ile Gln Lys Ala Phe Val Arg Lys Gln Lys Ala Leu Asp Glu Ile Lys
1025 1030 1035 1040

Pro Leu Glu Asp Leu Asn Asn Lys Lys Asp Ser Cys Ile Ser Asn His
1045 1050 1055

Thr Thr Ile Glu Ile Gly Lys Asp Leu Asn Tyr Leu Lys Asp Gly Asn
1060 1065 1070

Gly Thr Thr Ser Gly Ile Gly Ser Ser Val Glu Lys Tyr Val Val Asp
1075 1080 1085

Glu Ser Asp Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr
1090 1095 1100

Val Pro Ile Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu
1105 1110 1115 1120

Glu Phe Ser Ser Glu Ser Asp Met Glu Glu Ser Lys Glu Lys Leu Asn
1125 1130 1135

Ala Thr Ser Ser Ser Glu Gly Ser Thr Val Asp Ile Gly Ala Pro Ala
1140 1145 1150

Glu Gly Glu Gln Pro Glu Val Glu Pro Glu Glu Ser Leu Glu Pro Glu
1155 1160 1165

Ala Cys Phe Thr Glu Asp Cys Val Arg Lys Phe Lys Cys Cys Gln Ile
1170 1175 1180

Ser Ile Glu Glu Gly Lys Gly Lys Leu Trp Trp Asn Leu Arg Lys Thr
1185 1190 1195 1200

Cys Tyr Lys Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe
1205 1210 1215

Met Ile Leu Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile
1220 1225 1230

Glu Gln Arg Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val
1235 1240 1245

Phe Thr Tyr Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr
1250 1255 1260

Gly Phe Gln Val Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu

1265 1270 1275 1280

Ile Val Asp Val Ser Leu Val Ser Leu Thr Ala Asn Ala Leu Gly Tyr
1285 1290 1295

Ser Glu Leu Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg
1300 1305 1310

Pro Leu Arg Ala Leu Ser Arg Phe Glu Gly Met Arg Ala Val Val Asn
1315 1320 1325

Ala Leu Leu Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys
1330 1335 1340

Leu Ile Phe Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala
1345 1350 1355 1360

Gly Lys Phe Tyr His Cys Ile Asn Tyr Thr Thr Gly Glu Met Phe Asp
1365 1370 1375

Val Ser Val Val Asn Asn Tyr Ser Glu Cys Lys Ala Leu Ile Glu Ser
1380 1385 1390

Asn Gln Thr Ala Arg Trp Lys Asn Val Lys Val Asn Phe Asp Asn Val
1395 1400 1405

Gly Leu Gly Tyr Leu Ser Leu Leu Gln Val Ala Thr Phe Lys Gly Trp
1410 1415 1420

Met Asp Ile Met Tyr Ala Ala Val Asp Ser Arg Asn Val Glu Leu Gln
1425 1430 1435 1440

Pro Lys Tyr Glu Asp Asn Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe
1445 1450 1455

Ile Ile Phe Gly Ser Phe Phe Thr Leu Asn Leu Phe Ile Gly Val Ile
1460 1465 1470

Ile Asp Asn Phe Asn Gln Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile
1475 1480 1485

Phe Met Thr Glu Glu Gln Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu
1490 1495 1500

Gly Ser Lys Lys Pro Gln Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe
1505 1510 1515 1520

Gln Gly Met Val Phe Asp Phe Val Thr Lys Gln Val Phe Asp Ile Ser

1525 1530 1535

Ile Met Ile Leu Ile Cys Leu Asn Met Val Thr Met Met Val Glu Thr
1540 1545 1550

Asp Asp Gln Ser Gln Glu Met Thr Asn Ile Leu Tyr Trp Ile Asn Leu
1555 1560 1565

Val Phe Ile Val Leu Phe Thr Gly Glu Cys Val Leu Lys Leu Ile Ser
1570 1575 1580

Leu Arg Tyr Tyr Tyr Phe Thr Ile Gly Trp Asn Ile Phe Asp Phe Val
1585 1590 1595 1600

Val Val Ile Leu Ser Ile Val Gly Met Phe Leu Ala Glu Leu Ile Glu
1605 1610 1615

Lys Tyr Phe Val Ser Pro Thr Leu Phe Arg Val Ile Arg Leu Ala Arg
1620 1625 1630

Ile Gly Arg Ile Leu Arg Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr
1635 1640 1645

Leu Leu Phe Ala Leu Met Met Ser Leu Pro Ala Leu Phe Asn Ile Gly
1650 1655 1660

Leu Leu Leu Phe Leu Val Met Phe Ile Tyr Ala Ile Phe Gly Met Ser
1665 1670 1675 1680

Asn Phe Ala Tyr Val Lys Arg Glu Val Gly Ile Asp Asp Met Phe Asn
1685 1690 1695

Phe Glu Thr Phe Gly Asn Ser Met Ile Cys Leu Phe Gln Ile Thr Thr
1700 1705 1710

Ser Ala Gly Trp Asp Gly Leu Leu Ala Pro Ile Leu Asn Ser Gly Pro
1715 1720 1725

Pro Asp Cys Asp Pro Asp Lys Asp His Pro Gly Ser Ser Val Lys Gly
1730 1735 1740

Asp Cys Gly Asn Pro Ser Val Gly Ile Phe Phe Phe Val Ser Tyr Ile
1745 1750 1755 1760

Ile Ile Ser Phe Leu Val Val Val Asn Met Tyr Ile Ala Val Ile Leu
1765 1770 1775

Glu Asn Phe Ser Val Ala Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu

1780 1785 1790

Asp Asp Phe Glu Met Phe Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp
1795 1800 1805

Ala Thr Gln Phe Ile Glu Phe Ala Lys Leu Ser Asp Phe Ala Asp Ala
1810 1815 1820

Leu Asp Pro Pro Leu Leu Ile Ala Lys Pro Asn Lys Val Gln Leu Ile
1825 1830 1835 1840

Ala Met Asp Leu Pro Met Val Ser Gly Asp Arg Ile His Cys Leu Asp
1845 1850 1855

Ile Leu Phe Ala Phe Thr Lys Arg Val Leu Gly Glu Ser Gly Glu Met
1860 1865 1870

Asp Ala Leu Arg Ile Gln Met Glu Glu Arg Phe Met Ala Ser Asn Pro
1875 1880 1885

Ser Lys Val Ser Tyr Glu Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln
1890 1895 1900

Glu Glu Val Ser Ala Ile Ile Ile Gln Arg Ala Tyr Arg Arg Tyr Leu
1905 1910 1915 1920

Leu Lys Gln Lys Val Lys Lys Val Ser Ser Ile Tyr Lys Lys Asp Lys
1925 1930 1935

Gly Lys Glu Cys Asp Gly Thr Pro Ile Lys Glu Asp Thr Leu Ile Asp
1940 1945 1950

Lys Leu Asn Glu Asn Ser Thr Pro Glu Lys Thr Asp Met Thr Pro Ser
1955 1960 1965

Thr Thr Ser Pro Pro Ser Tyr Asp Ser Val Thr Lys Pro Glu Lys Glu
1970 1975 1980

Lys Phe Glu Lys Asp Lys Ser Glu Lys Glu Asp Lys Gly Lys Asp Ile
1985 1990 1995 2000

Arg Glu Ser Lys Lys
2005

<210> 37
<211> 912
<212> DNA

<213> Homo sapiens

<400> 37
gaattcttta tatgggttga atgactttct gacatagcaa ataaaaagca tgaggagaag 60
cattatctgt taacaaaatt aacacttaaa atcaacaaag ttttaatgtt tcgttccaag 120
aaaagcctgt ggaagatcag ttccacaact gagagctttg ggctgcttca gacatatgtc 180
tgtgtgtacg ctgtgaaggt gtttctcttc acagttcccc gccctctagt ggtagttaca 240
ataatgccat tttgtagtcc ctgtacagga aatgcctctt cttacttcag ttaccagaat 300
ccttttacag gaagttaggt gtggtctttg aaggagaatt aaaaaaaaaa aaaaaaaaaa 360
aaaaaagatt ttttttttt taaagcatga tggaatttta gctgcagtct tcttggggcc 420
agcttatcaa tcccaaactc tgggggtaaa agattctaca ggggtaatgt tttattattc 480
ttattatgct tattctctgt gatgcttctc tacctttaca gtagtagaat ccttggggaa 540
atctgcagag ggaccacttt cattttgaag ctgctggctg catgttttag catgtctctt 600
ctattagaga atccaggcat ggcagtttcc tcccccagtg tgcaaggacc atcttcatgc 660
ctatgtctgt cgctaggcat gagggtctct aggaatgggt gaaaaaaatg agggatgttt 720
tggaggcact ataatactgg ggagggcagt ctgctagctg gtagctgaaa ggtcctggtt 780
tacttcaaca ttttttttaa ataaaactgt gcagtagttt ttgttatttt agggttccct 840
ctgttttatc tggtgtatgc tgcagaagtg aactgcataa cacatttcac tcttagaaat 900
gcattccata ta 912

<210> 38
<211> 722
<212> DNA
<213> Homo sapiens

<400> 38
ctcagtgcat gtaactgaca caatcacctc tatctaatgg tcatgcttct tacctcctgt 60
tctgtagcac tttcttatgc aaggagctaa acagtgatta aaggagcagg atgaaaagat 120
ggcacagtca gtgctggtac cgccaggacc tgacagcttc cgcttcttta ccagggaatc 180
ccttgctgct attgaacaac gcattgcaga agagaaagct aagagaccca aacaggaacg 240
caaggatgag gatgatgaaa atggcccaaa gccaaacagt gacttggaag cagsaaaatc 300
tcttccattt atttatggag acattcctcc agagatggtg tcagtgcccc tggaggatct 360
ggacccctac tatatcaata agaaagtgag ttcttagtca agttgccttc actgcctatt 420
tactaattgg ttctgggcta gtcccaggga tgatggtgaa gaaggctggc ctccttccct 480
ctgtctaaag tatcactaag atgctggatg ggcctgaccg tgtaatggac caatgatcct 540
agaagtcttt tggaagcact catttgaacc tgcatttgtg agacaggcag agaactggtg 600
aggcatcctc cagcgcggga attaaggaag gacaaaagcc tattcacctt cttgaataca 660
aattatatgc ttaaaccagt gtaaattgac cctgattccc taataatgtt gagaagcaaa 720
aa 722

<210> 39
<211> 561
<212> DNA
<213> Homo sapiens

<400> 39

cctatggcat tgatcacaaa ttttcttaat aatcctcatg tcatttatca aatttaggaa 60...
agtttatagt gctcagaaaa aaaaagcatc tatcttcatg tcatatgatg gtaattatta 120
tgttatacac tattttacag ggcaatattt ataaataatg gttttacttt tctcttaaaa 180
tattcttaat atatattcta agttttgttt tatgtgttgt gttttctttt tcagacgttt 240
atagtattga ataaagggaa agcaatctct cgattcagtg ccacccctgc cctttacatt 300
ttaactccct tcaaccctat tagaaaatta gctattaaga ttttggtaca ttcatatcct 360
ttttcaaatc gtcacttaat atgattttct tctttgacca agttattgag ctacacattt 420
tccaaaatat ctgtggttgg caatgttatg tgttctttct ttttctttcc ttttactcaa 480
tcgttagcat gttgcaaaat gagatcacag gtaagtgaat tactttcccc cgtcttctaa 540
gtgtttcttc tctacccaac t 561

<210> 40
<211> 510
<212> DNA
<213> Homo sapiens

<400> 40
acctaaatag cctcaaaata gttgatggct tggcctgaag acaagatcta aatatgaggt 60
tgctgagtta tagaaatggc aaaaaaaagg gtcaataata gaataataag caacaaaata 120
atagtaagca ctaaagtttt aaacttcatg gtggtgaagg catggtagtg cataaaagta 180
agatttttcc attgaacttt gtcttccttg acgatattct actttattca atatgctcat 240
tatgtgcacg attcttacca actgtgtatt tatgaccatg agtaaccctc cagactggac 300
aaagaatgtg gagtaagtat aaatattttt caatattgac ctccctttat gtttcatatt 360
gtgcttttaa caccttgaga cctcctcaat ttctttaaca aatcatgcta gctactgtta 420
accagaccct gattcaaatt catttctgtc actaaatgtc ttctaggaca aagcttgtag 480
tgggctcact tagttgtgta aattactgca 510

<210> 41
<211> 370
<212> DNA
<213> Homo sapiens

<400> 41
taagatatgt acttgtaaat taaccactag atttttaatg tgagcttggc tattgtctct 60
caggtatacc tttacaggaa tttatacttt tgaatcactt attaaaatac ttgcaagggg 120
cttttgttta gaagatttca catttttacg ggatccatgg aattggttgg atttcacagt 180
cattactttt gcgtaagtat cttaatacat tttctatcct ggaagagtaa atcactggtg 240
ggagcctata ctatattttc cttggtggct tgccttgaca gaccaagcat ttntcttagt 300
aatcatagtt ttcttccaat caaattatcc agtttggaga aattaggaac tatcatagta 360
aattacatgg 370

<210> 42
<211> 370
<212> DNA
<213> Homo sapiens

<400> 42
caattagcac tgtaaagtaa taaagtttcc caaataacag agattatgat tgatgacaat 60
gccattttcc tcttaattgg gaaagctgat ggcgacactc atgaaattaa aaaggtcttg 120
atgaaagacc aangaagacg tagatttccc taaattctga ataactctga tttaattcta 180
caggtatgta acagaatttg taaacctagg caatgtttca gctcttcgaa ctttcagagt 240
cttgagagct ttgaaaacta tttctgtaat tccaggtaag aagaaaatgg tataaggtgg 300
taggcccctt atatctccaa ctgtttcttg tgttctgtca ttgtgtttgt gtgtgaaccc 360
cctattacag 370

<210> 43
<211> 410
<212> DNA
<213> Homo sapiens

<400> 43
gtaagaagaa aatggtataa ggtggtaggc cccttatatc tccaactgtt tcttgtgttc 60
tgtcattgtg tttgtgtgtg aacccccctat tacagatatg tgacagagtt tgtggacctg 120
ggcaatgtct cagcgttgag aacattcaga gttctccgag cattgaaaac aatttcagtc 180
attccaggtg agagctaggt taaacaccga ggctgacttt agctacagtg gtgctacaat 240
cacagctttt gtgcagaagc cttgttgcta gttgcatatt gcaaataaat atgtaaaaaa 300
gcaagaattg gtacatcatt ttttggatgg atttgattct ttgcttttta cccgttgctt 360
tctttaaaac tattctaaat cagcctttga gtttaacaag tgttgcatga 410

<210> 44
<211> 1066
<212> DNA
<213> Homo sapiens

<400> 44
aaagagtgtt tggaaataca catttggttc atttccattc acagttttct aatgaacata 60
caagttctgc tttcattcat tttcaccagc tagtaggctt ttcatgaaaa tgttattcaa 120
tcacaaacat taaactaata ttgttggcat tctgcatgac atttttattt tccaggccaa 180
gctcatgata tttttgccgg taaaatagct gttgagtagt atatttaant tccccccttct 240
gattttgttt gtaggcctga agaccattgt gggggccctg atccagtcag tgaagaagct 300
ttctgatgtc atgatcttga ctgtgttctg tctaagcgtg tttgcgctaa taggattgca 360
gttgttcatg ggcaacctac gaaataaatg tttgcaatgg cctccagata attcttcctt 420
tgaaataaat atcacttcct tctttaacaa ttcattggat gggaatggta ctactttcaa 480
taggacagtg agcatattta actgggatga atatattgag gataaaagta agatatactc 540
tataaaccat taagttgttt agttctctaa atattaaata ttatatataa tggaaattat 600
ctcaatttag atgtgaatca agtgacttag actaatttaa gatgatttaa tacatataaa 660
agagatatca aaggatacct tattctattt ttsttatctg tccattgata tagtaaaagt 720
tctcatttga aaatgtgttg tcttatactc atgttgaaag taatttcata ttatgccata 780
ttaaaaaagg tttatttggt agacattaat caggtttttc agtcatttta ataaataagt 840
cagtagtttg aactattcmg cgtattccac tgaaatgtcg ttaagaagac tgaggggaaa 900
taatttggcc ctatttggtt gatgcaacat atgtattgag tacatatgct atatctgaaa 960

ctagagaaac catttatcaa gatgaaataa gaatttgtgt gctcctcaga aggttaagta 1020
accctgattt agccattcac ttcatccata ttctaattag tccctt 1066

<210> 45
<211> 385
<212> DNA
<213> Homo sapiens

<400> 45
gttcaattat tgtgaaaaat cttctttagc catatatatt tattagttta tccatctcat 60
tatgattgaa aacatttgtg agctttgcca cctaaacagg gtggctgaag tgttttacag 120
gattttaatg attctttcta ttcctttctc tttaaatagg tcacttttat tttttacagg 180
ggcaaaatga tgctctgctt tgtggcaaca gctcagatgc agggtaagtg tatgcttcct 240
actgagtttc agtccacact gctccatcag tgtcaataac ctgccacctc ccactcatcc 300
agtcccacca ctcctcactc aaaaccctcc ataaattcta cttcacggtg actctcagaa 360
tgaccaggat aagtgtagat tctca 385

<210> 46
<211> 430
<212> DNA
<213> Homo sapiens

<400> 46
tataataatg acaattatga atcacagagg aatccacaaa gtagacctta tagattctgt 60
cattatataa atcagtccac ttagtgctga gttaagtact gggtaaggtg agagaaatcg 120
gctttttttct agtgcctgta taaaacagac attggcatat attaaaacag gaaaaccaat 180
tagcagactt gccgttattg actycctctc tttcctctaa cctaattaca gccagtgtcc 240
tgaaggatac atctgtgtga aggctggtag aaaccccaac tatggctaca cgagctttga 300
caccttttagt tgggcctttt tgtccttatt tcgtctcatg actcaagact tctgggaaaa 360
cctttatcaa ctggtgagaa cagataaaat catttttctg agaatcataa aacaccgaac 420
tcaagagaat 430

<210> 47
<211> 646
<212> DNA
<213> Homo sapiens

<400> 47
tgctgtagaa tattttatta cttagagtgt aagtttgtaa catcctatat aaaatttatt 60
aaaatctctc ttccattttg cagacactac gtgctgctgg gaaaacgtac atgatatttt 120
ttgtgctggt cattttcttg ggctcattct atctaataaa tttgatcttg gctgtggtgg 180
ccatggccta tgaggaacag aatcaggcca cattggaaga ggctgaacag aaggaagctg 240
aatttcagca gatgctcgaa cagttgaaaa agcaacaaga agaagctcag gtatagtgaa 300
caagcatacg gtcctttgtt tttctgtatc taaattcttt aacctaaatg ttgaggtcag 360
tggcaaggta gttgacatta gaaataggtc atatgtgttt ggtaagtgct aggagcctgt 420

ttggttatta agaagttatt actttattgc aatgatctct gtcaatagtg tcaatagtaa 480
tggcatcaaa aaatggataa ttataattgc tttactgaca ttttttttctc ccttgtgact 540
ccttgaggaa attaatgatt aacaaaggcc tcatgtactc aaacttgcag agtagataaa 600
cctacatgtc ctcagttgaa gtattttctt aggggaagag gaattc 646

<210> 48
<211> 711
<212> DNA
<213> Homo sapiens

<400> 48
tatgtatcat cttccatatg aatgcgcatt ttactctttg attggtctaa taacagtgta 60
ctgtgttcta aaacacagaa taaaatggag aattgttttt caagattatc ttcatgatat 120
tgaagctcaa ttaagcagta acatgataat tatttttaa gatnatatgc aacttcccac 180
atactttgcg cccttctagg cggcagctgc agccgcatct gctgaatcaa gagacttcag 240
tggtgctggt gggataggag ttttttcaga gagttcttca gtagcatcta agttgagctc 300
caaaagtgaa aaagagctga aaaacagaag aaagaaaaag aaacagaaag aacagtctgg 360
agaagaagag aaaaatgaca gagtcctaaa atcggaatct gaagacagca taagaagaaa 420
aggtttccgt ttttccttgg aaggaagtag gctgacatat gaaaagagat tttcttctcc 480
acaccaggta aaaatattaa attacatgaa ttgtgttctc ataaattttt taaaagaata 540
tgccagaatt taatggagag aaaaccgcct tccacctgga tggcacaatg ctttcagagt 600
agtgatgatt atcaagtgtt ttggctatca cttcagagaa tttgtgagtt ttgcaacttt 660
ttggaatccc aggaaggaaa ttttagatcc ctctgggttt ggaaaaattt g 711

<210> 49
<211> 1026
<212> DNA
<213> Homo sapiens

<400> 49
ttatggggac acttctgact atgttgaggt gtgggtaaag taggagaaaa gagagcagaa 60
gatggaaaat ggaggaagga gaaaaagcga gagtgaaata gaaaaggtga accttgtaga 120
aagtgccaaa atgccaccag cagtcatcag aggggtgctt tcttccacat gtccaatgac 180
ttatccttga gtaagtcaat gactatgaca caatgaatca aattctgttt ttcagaatgc 240
cagctcttaa ctctcttcat ctcatttttg tttcttttct tgttattcat agtccttact 300
gagcatccgt ggctcccttt tctctccaag acgcaacagt agggcgagcc ttttcagctt 360
cagaggtcga gcaaaggaca ttggctctga gaatgacttt gctgatgatg agcacagcac 420
ctttgaggac aatgacagcc gaagagactc tctgttcgtg ccgcacagac atggagaacg 480
gcgccacagc aatgtcagcc aggccagccg tgcctccagg gtgctcccca tcctgcccat 540
gaatgggaag atgcatagcg ctgtggactg caatggtgtg gtctccctgg tcgggggccc 600
ttctaccctc acatctgctg ggcagctcct accagaggtg aggccaacyy magattgcag 660
ctgatgtgaa gagagttgtg actggtgcag gcaggagtgy ttttccattt mcacatctaa 720
gaatttkttg agtttsttgc ccaaaggctg ggagtttgtt caatcaagct gttaactgtc 780
ttgtgaaact sttctattca gactttycta caaagtaatt aaaaacctag gttggctgtc 840
agagaatata attagamgtm atctttcatc ayyattacta tggtatgaaa ctcgccaaaa 900
agcaaagcaa caatttatca agcataatgt tygaytaata tagttaaatt aaatccaagg 960

aaattaatgc tcacaaatta aataaatact taaggatttt gtgattgttg ttcatttaaa 1020
aggaga 1026

<210> 50
<211> 601
<212> DNA
<213> Homo sapiens

<400> 50
ataggaaagc ccaccttgac aaacccaggg ctccccaaaa gctgaaaatc tgacagactt 60
taaacaaccc ccaaataatt atcattccaa caatatctta gtgagctttt tacatctgag 120
aaagcatggt gtatatttag ttaaataaca cctgttgtag gaatgctttg ggctttgctg 180
ctttcaaaaa tagtggttat ttcatctgaa attctacttc tagggcacaa ctactgaaac 240
agaaataaga aagagacggt ccagttctta tcatgtttcc atggatttat tggaagatcc 300
tacatcaagg caaagagcaa tgagtatagc cagtattttg accaacacca tggaaggtat 360
gttaaaagtc ctgcgtcaca gttacttggt gctttcctaa tgatgaaaaa cacttcataa 420
atttcaataa aatacttcct gacttgatat tgtatcatta ttacacattt tactaaataa 480
cagtaaaatc cgtgcataac tcatggattc atatattcca cagatttttt ttttttatat 540
ttagcctgta gaaagctgct gcaaatgtaa ggtatatttg aacaccactt tcataactta 600
a 601

<210> 51
<211> 645
<212> DNA
<213> Homo sapiens

<400> 51
gcttactagc ctttctgtac tgatcctttc tatgacagca aacccattgt aaaattttcc 60
ctgttcctcc agcagattaa cccataatat cttttaacaa ctttagattt tttaaattcc 120
ttttaattta aaccaaatct gcttaataga aagtaagcag ttttcatgag gattctaact 180
ttttttcttc cagaacttga agaatccaga cagaaatgcc caccatgctg gtataaattt 240
gctaatatgt gtttgatttg ggactgttgt aaaccatggt taaaggtgaa acaccttgtc 300
aacctggttg taatggaccc atttgttgac ctggccatca ccatctgcat tgtcttaaat 360
acactcttca tggctatgga gcactatccc atgacggagc agttcagcag tgtactgtct 420
gttggaaacc tggtaagcct cactgagagt ttctcttcct cttgaaagag tttataattg 480
ccttagtgaa ttttacatat tgctctcaaa ttaaatatca actaattggc catgtatatc 540
ttgacatcaa atgtttagca tccctttaa ataacaaaaa aatgttgcta ccatagtgca 600
aaagagtcaa agaatttatg tacaatttga tttagaattg aattt 645

<210> 52
<211> 485
<212> DNA
<213> Homo sapiens

<400> 52

tggcccaaac caatttttaa atcaggaatt taatttwtat attgttggga gttaaattaa 60
gttgctcaat aattattcgt gtttcaakas tatttgctca tataatgaac tacacttctc 120
atttaggtct tcacagggat cttcacagca gaaatgtttc tcaagataat tgccatggat 180
ccatattatt actttcaaga aggctggaat atttttgatg gttttattgt gagccttagt 240
ttaatggaac ttggtttggc aaatgtggaa ggattgtcag ttctccgatc attccggctg 300
gtaaattaac tgggagtgtt cataaaatgt actttrtaat taattagtct tcattctcat 360
ctagtaaaaa tggcaagatt tcccatcatt ataatatatt tgaatacctt ctaaaacaga 420
ttggattgcc ataccaccaa atggtagttt cttcttcatc atagctttaa taaagttcac 480
ttaaa 485

<210> 53
<211> 602
<212> DNA
<213> Homo sapiens

<400> 53
acagatttcc tcctgtgtcc atgtgactaa cccattgtgc acatgtaccc taaaaattag 60
tatataataa taaaataaaa taaaaataaa aataaaaaaa taaaaataaa ataaaattgc 120
agatttttt agaaatgcag agattaacac tgttcttgct tttatttcca gctccgagtt 180
ttcaagttgg caaaatcttg gccaactcta aatatgctaa ttaagatcat tggcaattct 240
gtgggggctc taggaaacct caccttggta ttggccatca tcgtcttcat ttttgctgtg 300
gtcggcatgc agctctttgg taagagctac aaagaatgtg tctgcaagat ttccaatgat 360
tgtgaactcc cacgctggca catgcatgac tttttccact ccttcctgat cgtgttccgc 420
gtgctgtgtg gagagtggat agagaccatg tgggactgta tggaggtcgc tggccaaacc 480
atgtgcctta ctgtcttcat gatggtcatg gtgattggaa atctagtggt atgtagcaaa 540
aacattttcc tcattttcat taaaaataat gtaatcatta aaaagtgttc aactgaagaa 600
ta 602

<210> 54
<211> 803
<212> DNA
<213> Homo sapiens

<400> 54
gtttcattta gcaatgattt cagtattttc tgcaatgact aataagcaaa tagtgataat 60
agtattattt tatattgacc aagcattttt atttcattca ctttttttca gaatagtgta 120
tcatgaatta gcagaaatgc atgttagaat aaaataaggt gtcaagaaca atcttagaaa 180
actaatgatg gaaagcaatt gaagcaatag aatgttttga tcacctgttt ttcctgctgt 240
gtttcaggtt ctgaacctct tcttggcctt gcttttgagt tccttcagtt ctgacaatct 300
tgctgccact gatgatgata acgaaatgaa taatctccag attgctgtgg gaaggatgca 360
gaaaggaatc gattttgtta aaagaaaaat acgtgaattt attcagaaag cctttgttag 420
gaagcagaaa gctttagatg aaattaaacc gcttgaagat ctaaataata aaaaagacag 480
ctgtatttcc aaccatacca ccatagaaat aggcaaagac ctcaattatc tcaaagacgg 540
aaatggaact actagtggca taggcagcag tgtagaaaaa tatgtcgtgg atgaaagtga 600
ttacatgtca tttataaaca accctagcct cactgtgaca gtaccaattg ctgttggaga 660
atctgacttt gaaaatttaa atactgaaga attcagcagc gagtcagata tggaggaaag 720

caaagaggta aaatgttaaa taaggagata ttttggtgta tataatctgt gttaaatatc 780
aggtgtttaa tgcgtgtctc tgt 803

<210> 55
<211> 615
<212> DNA
<213> Homo sapiens

<400> 55
atctctatac taggctcaaa cagaagttat ttccgttgtt agcaccatat ttttaaaaga 60
aaaaaaaata ctatggtgtt gtatctaatn ttgtgacccc tgacctttac caaagcggat 120
tggcattatg tttaagttct taattacaga tcaagaaaaa tgcatacaga agatgggggg 180
gggcacacct aattaatttt tatatttaga ttaaagaaaa taattaaatg tgtttttttg 240
tgggattgat tttcagaagc taaatgcaac tagttcatct gaaggcagca cggttgatat 300
tggagctccc gccgagggag aacagcctga ggttgaacct gaggaatccc ttgaacctga 360
agcctgtttt acagaagnnn nnnnnnaagc aaaacaataa catatgtggt cttgagtatc 420
ctcttttcta cccatttttt cctatttatt taaatgtctg tttatttgtc taccatctag 480
ttcatctatc tatctgtatc tatctatcta tctatctatc tagtaatcat ctatacctat 540
ccaacaactg tacatttatt tgtttttttt ttttgcattt gctgtttgaa aaaaaatgca 600
acgttttaaa ggcaa 615

<210> 56
<211> 400
<212> DNA
<213> Homo sapiens

<400> 56
gatagctttt gtaagcggaa gctatcttaa aaattaatgt tatttacaat gtattatcag 60
gtaataatgt aaatgaatct cccaccaaca caaatatacc taatcaaaga gtaatttttt 120
gtcttcattt ttttcccaca tattttagac tgtgtacgga agttcaagtg ttgtcagata 180
agcatagaag aaggcaaagg gaaactctgg tggaatttga ggaaaacatg ctataagata 240
gtggagcaca attggttcga aaccttcatt gtcttcatga ttctgctgag cagtggggct 300
ctggtaggtg atgcatgatc cactccttca cctttcatct gaaatctttt ccctttccct 360
tcaatcaact catattaccc acttttaaat taaggtgttt 400

<210> 57
<211> 560
<212> DNA
<213> Homo sapiens

<400> 57
aaattactga aacccttggt tgactgaaat gcccagtcag cagtcattta tgatcagata 60
atgataaagt aaaattcagc catgggaaac attaaacctt ccagccttag gcacctgata 120
agagcttgca tcgtttcctt ttttaagaaa tcatcaatta gagactgttt ctgatcataa 180
aatttaatag aatttttga cttacaggcc tttgaagata tatacattga gcagcgaaaa 240

accattaaga ccatgttaga atatgctgac aaggttttca cttacatatt cattctggaa 300
atgctgctaa agtgggttgc atatggtttt caagtgtatt ttaccaatgc ctggtgctgg 360
ctagacttcc tgattgttga tgtgagtatg ctgcactttg ctgctttatt cattggcata 420
tatgtaatag ttctagcaat ggtgcctgac acagtgtagg cactcagtaa cactgtatca 480
gcccaaatat aaattatgtt tctcatttca cagtgagagg atgcctcaaa acatttttta 540
ccaatttaaa tacatataca 560

<210> 58
<211> 480
<212> DNA
<213> Homo sapiens

<400> 58
aaattcttag gcctttcccc aaacttacta agtcagactc tgctattggt gtttttaaca 60
agacccctgg gtgattttga aactcatgaa agttcgagaa ttactgattc attgcataga 120
gcaaggctga actgtgtaga catttttata tgtaaataag aaaattgtgt tgcttttttct 180
gtataggtct cactggttag cttaactgca aatgccttgg gttactcaga acttggtgcc 240
atcaaatccc tcagaacact aagagctctg aggccactga gagctttgtc ccggtttgaa 300
ggaatgaggg taagactgaa tgccttagag tttgtcagaa ttattattga gagcagactg 360
acactttgta ccatggaaat gtcaaattta tggagaattt gtgtcttaca cattcatact 420
gacatagcta atcaatcaaa aataatattt accagatgcc cataatactt ggcactgctg 480

<210> 59
<211> 640
<212> DNA
<213> Homo sapiens

<400> 59
taattttaaa attcttagtt ggagctacca gagtctagtt tctacccaat attcaacttt 60
gaaacagatt tttttaatca tttgactgtt cttttaataa tgtttaaaaa taagtaaata 120
tttgttgttg gcttttcact tatttttcct tctcatcctg tgccaggttg ttgtaaatgc 180
tcttttagga gccattccat ctatcatgaa tgtacttctg gtttgtctga tcttttggct 240
aatattcagt atcatgggag tgaatctctt tgctggcaag ttttaccatt gtattaatta 300
caccactgga gagatgtttg atgtaagcgt ggtcaacaac tacagtgagt gcaaagctct 360
cattgagagc aatcaaactg ccaggtggaa aaatgtgaaa gtaaactttg ataacgtagg 420
acttggatat ctgtctctac ttcaagtagt aagtaatcac tttattattt tccatgatgt 480
gtaattaaaa tgagtctaaa gtttttcttc ctcataatga gatatccacc tgttagaatg 540
gctattatca aacagataaa tgacaataaa tgctggcaag aatgtgaaga aaagggaacc 600
cttgtacatt gttggcaggg atgtaaatta gtatagcttt 640

<210> 60
<211> 480
<212> DNA
<213> Homo sapiens

<400> 60
atttgaagta ttttcaatgc atatcgcaaa acattgcccc aaaagtgaat acaaatttca 60
agcttattta tatgcctgta ttgaatacat gtcaaataga attttgatca attattcaat 120
ttatttttcta aaattataat tttgggaaaa aagaaaatga tatgactttt cttacaggcc 180
acgtttaagg gatggatgga tattatgtat gcagctgttg attcacgaaa tgtaagtcta 240
gttagaggga aattgtttag tttgattaaa tgtatatttc tacaatattg taatttagtg 300
atattgtcaa taaaataaaa ttatgtgctt aatttataaa acccatctat attataagga 360
taaaatattt aatcatacta tttctttcaa aattatcata ggatgatttt ctctaatcac 420
tctgtatctt ttaacatatc ttttctagta tttagcaagg cacctgacac aaaactttat 480

<210> 61
<211> 366
<212> DNA
<213> Homo sapiens

<400> 61
taaaacatgc ttagataatt aaaaactcac tgatgtactt tttgtgaaac aagtactaga 60
tataatggtt acaattcttc atattcttta ggtagaatta caacccaagt atgaagacaa 120
cctgtacatg tatctttatt ttgtcatctt tattattttt ggttcattct ttaccttgaa 180
tcttttcatt ggtgtcatca tagataactt caaccaacag aaaaagaaga taagtatatt 240
aaaacttcat ccttgctctg aaatatgaac taaatatttc atactctttc ctttagcctc 300
caaaatgcaa tcaccaaaaa aagaatataa aattcagaaa ttattttgag acatttgata 360
atcgat 366

<210> 62
<211> 560
<212> DNA
<213> Homo sapiens

<400> 62
tcgataagct tttaagcaat taataattca gatagcatgt ttttgatatt tttagtctag 60
aaatatgact aatatggcat aatttatata ttgaataaag gcatctctat aaatacagat 120
attagtaaca atagaatgaa atgtgggagc caatttttcac atgattacta aggtggattt 180
tatagccagc aaagaacaca attttaacaa gtgttgcttt catttcttta ctttggaggt 240
caagacattt ttatgacaga agaacagaag aaatactaca atgcaatgaa aaaactgggt 300
tcaaagaaac cacaaaaacc catacctcga cctgctgtaa gaataacata ttttcattgc 360
ctgttaaaac tatattacct aaccgtttca cagcccgaat ttctagaaac tagttatttt 420
tgtggatttg taacacaaag ttttttacct taacaatggg actagctagc ctaaatagct 480
tgaaaaatgt actttacata tataatatgt ataaattata taatgcataa catattttat 540
atgtaaacat ataaaataca 560

<210> 63
<211> 650
<212> DNA
<213> Homo sapiens

<400> 63
gttttgcaag gaatttttt ttttgtaaaa tgttgtgagg attaaagatg tgtttttata 60
aaagctacat tttttgttgc tttcttaaaa tcagaagaat tgaattcgat tttttttaag 120
gtttctaatg gaacttttac atattatttg ttccagaaca aattccaagg aatggtcttt 180
gattttgtaa ccaaacaagt ctttgatatc agcatcatga tcctcatctg ccttaacatg 240
gtcaccatga tggtggaaac cgatgaccag agtcaagaaa tgacaaacat tctgtactgg 300
attaatctgg tgtttattgt tctgttcact ggagaatgtg tgctgaaact gatctctctt 360
cgttactact atttcactat tggatggaat atttttgatt ttgtggtggt cattctctcc 420
attgtaggta agaagaggtg cttttattca gttaaggaat atagtggtaa aaatatgtgt 480
tttaaaactt tagaggtgtt tttcactaat ctttctcatt catcccaaac tcccaaataa 540
aaatctaata gtccattgtt ttagttttag tttgccattt ctctaattgc atgctgtgct 600
tgaaatgatg agtggaatac aaggaattta tattttcagc tttcatttat 650

<210> 64
<211> 3700
<212> DNA
<213> Homo sapiens

<400> 64
aatgttataa caccaaacat accagtttca ttttgctcaa caaacattgc agattatttg 60
catatataca tgtacctaac tgtcctgttc acattttgta aaactaatgt acttatgtaa 120
actttcattt gctactatta agtataacaa tatttttgtt atttgttgat tttctacagg 180
aatgtttctg gctgaactga tagaaaagta ttttgtgtcc cctaccctgt tccgagtgat 240
ccgtcttgcc aggattggcc gaatcctacg tctgatcaaa ggagcaaagg ggatccgcac 300
gctgctcttt gctttgatga tgtcccttcc tgcgttgttt aacatcggcc tccttctttt 360
cctggtcatg ttcatctacg ccatctttgg gatgtccaat tttgcctatg ttaagaggga 420
agttgggatc gatgacatgt tcaactttga gacctttggc aacagcatga tctgcctgtt 480
ccaaattaca acctctgctg gctgggatgg attgctagca cctattctta atagtggacc 540
tccagactgt gaccctgaca aagatcaccc tggaagctca gttaaaggag actgtgggaa 600
cccatctgtt gggattttct tttttgtcag ttacatcatc atatccttcc tggttgtggt 660
gaacatgtac atcgcggtca tcctggagaa cttcagtgtt gctactgaag aaagtgcaga 720
gcctctgagt gaggatgact ttgagatgtt ctatgaggtt tgggagaagt ttgatcccga 780
tgcgacccag tttatagagt ttgccaaact ttctgatttt gcagatgccc tggatcctcc 840
tcttctcata gcaaaaccca acaaagtcca gctcattgcc atggatctgc ccatggtgag 900
tggtgaccgg atccactgtc ttgacatctt atttgctttt acaaagcgtg ttttgggtga 960
gagtggagag atggatgccc ttcgaataca gatggaagag cgattcatgg catcaaaccc 1020
ctccaaagtc tcttatgagc ccattacgac cacgttgaaa cgcaaacaag aggaggtgtc 1080
tgctattatt atccagaggg cttacagacg ctacctcttg aagcaaaaag ttaaaaaggt 1140
atcaagtata tacaagaaag acaaaggcaa agaatgtgat ggaacaccca tcaaagaaga 1200
tactctcatt gataaactga atgagaattc aactccagag aaaaccgata tgacgccttc 1260
caccacgtct ccaccctcgt atgatagtgt gaccaaacca gaaaaagaaa aatttgaaaa 1320
agacaaatca gaaaaggaag acaaagggaa agatatcagg gaaagtaaaa agtaaaaaga 1380
aaccaagaat tttccatttt gtgatcaatt gtttacagcc cgtgatggtg atgtgtttgt 1440
gtcaacagga ctcccacagg aggtctatgc caaactgact gtttttacaa atgtatactt 1500
aaggtcagtg cctataacaa gacagagacc tctggtcagc aaactggaac tcagtaaact 1560
ggagaaatag tatcgatggg aggtttctat tttcacaacc agctgacact gctgaagagc 1620

agaggcgtaa tggctactca gacgatagga accaatttaa agggggggagg gaagttaaat 1680
ttttatgtaa attcaacatg tgacacttga taatagtaat tgtcaccagt gtttatgttt 1740
taactgccac acctgccata tttttacaaa acgtgtgctg tgaatttatc acttttcttt 1800
ttaattcaca ggttgtttac tattatatgt gactattttt gtaaatgggt ttgtgtttgg 1860
ggagagggat taaagggagg gaattctaca tttctctatt gtattgtata actggatata 1920
ttttaaatgg aggcatgctg caattctcat tcacacataa aaaaatcaca tcacaaaagg 1980
gaagagttta cttcttgttt caggatgttt ttagattttt gaggtgctta aatagctatt 2040
cgtattttta aggtgtctca tccagaaaaa atttaatgtg cctgtaaatg ttccatagaa 2100
tcacaagcat taaagagttg ttttatttt acataaccca ttaaatgtac atgtatatat 2160
gtatatatgt atatgtgcgt gtatatacat atatatgtat acacacatgc acacacagag 2220
atatacacat accattacat tgtcattcac agtcccagca gcatgactat cacatttttg 2280
ataagtgtcc tttggcataa aataaaaata tcctatcagt cctttctaag aagcctgaat 2340
tgaccaaaaa acatccccac caccacttta taaagttgat tctgctttat cctgcagtat 2400
tgtttagcca tcttctgctc ttggtaaggt tgacatagta tatgtcaatt taaaaaataa 2460
aagtctgctt tgtaaatagt aattttaccc agtggtgcat gtttgagcaa acaaaaatga 2520
tgatttaagc acactactta ttgcatcaaa tatgtaccac agtaagtata gtttgcaagc 2580
tttcaacagg taatatgatg taattggttc cattatagtt tgaagctgtc actgctgcat 2640
gtttatcttg cctatgctgc tgtatcttat tccttccact gttcagaagt ctaatatggg 2700
aagccatata tcagtggtaa agtgaagcaa attgttctac caagacctca ttcttcatgt 2760
cattaagcaa taggttgcag caaacaagga agagcttctt gctttttatt cttccaacct 2820
taattgaaca ctcaatgatg aaaagcccga ctgtacaaac atgttgcaag ctgcttaaat 2880
ctgtttaaaa tatatggtta gagttttcta agaaaatata aatactgtaa aaagttcatt 2940
ttatttttatt tttcagcctt ttgtacgtaa aatgagaaat taaaagtatc ttcaggtgga 3000
tgtcacagtc actattgtta gtttctgttc ctagcacttt taaattgaag cacttcacaa 3060
aataagaagc aaggactagg atgcagtgta ggtttctgct tttttattag tactgtaaac 3120
ttgcacacat ttcaatgtga aacaaatctc aaactgagtt caatgtttat ttgctttcaa 3180
tagtaatgcc ttatcattga aagaggctta aagaaaaaaa aaatcagctg atactcttgg 3240
cattgcttga atccaatgtt tccacctagt ctttttattc agtaatcatc agtcttttcc 3300
aatgtttgtt tacacagata gatcttattg acccatatgg cactagaact gtatcagata 3360
taatatggga tcccagcttt ttttcctctc ccacaaaacc aggtagtgaa gttatattac 3420
cagttacagc aaaatacttt gtgtttcaca agcaacaata aatgtagatt ctttatactg 3480
aagctattga cttgtagtgt gttggtgaat gcatgcagga agatgctgtt accataaaga 3540
acggtaaacc acattacaat caagccaaag aataaaggtt cgcttatgta tatgtattta 3600
attgttgtct ttgtttctat ctttgaaatg ccatttaaag gtagatttct atcatgtaaa 3660
aataatctat ctgaaaaaca aatgtaaaga acacacatta 3700

<210> 65
<211> 9112
<212> DNA
<213> Homo sapiens

<400> 65
accatagagt gaatctcaga acaggaagcg gaggcataag cagagaggat tctggaaagg 60
tctctttgtt ttcttatcca cagagaaaga aagaaaaaaa attgtaacta atttgtaaac 120
ctctgtggtc aaaaaaaaaa aaaaaaaaaa aagctgaaca gctgcagagg aagacacgtt 180
ataccctaac catcttggat gctgggcttt gttatgctgt aattcataag gctctgtttt 240
atcagagatt atggagcaag aaaactgaag ccaagccaca tcaaggtttg acagggatga 300

gatacctgtc aaggattcat agtagagtgg cttactggga aaggagcaaa gaatctcttc 360
tagggatatt gtaagaataa atgagataat tcacagaagg gacctggagc ttttccggaa 420
aaaggtgctg tgactatcta aggggaaaag ctgagagtct ggaactagcc tatcttccga 480
ggacttagag acaacagtat gggaatttca acgagacgtt tttactttct tttgaccaag 540
attcaaattc tttattccag cccttgataa gtaaataaga aggtaattcg tatgcaagaa 600
gctacacgta attaaatgtg caggatgaaa agatggcaca ggcactgttg gtacccccag 660
gacctgaaag cttccgcctt tttactagag aatctcttgc tgctatcgaa aaacgtgctg 720
cagaagagaa agccaagaag cccaaaaagg aacaagataa tgatgatgag aacaaaccaa 780
agccaaatag tgacttggaa gctggaaaga accttccatt tatttatgga gacattcctc 840
cagagatggt gtcagagccc ctggaggacc tggatcccta ctatatcaat aagaaaactt 900
ttatagtaat gaataaagga aaggcaattt cccgattcag tgccacctct gccttgtata 960
ttttaactcc actaaaccct gttaggaaaa ttgctabsaa gattttggta cattctttat 1020
tcagcatgct tatcatgtgc actattttga ccaactgtgt atttatgacc ttgagcaacc 1080
ctcctgactg gacaaagaat gtagagtaca cattcactgg aatctatacc tttgagtcac 1140
ttataaaaat cttggcaaga gggttttgct tagaagattt tacgtttctt cgtgatccat 1200
ggaactggct ggatttcagt gtcattgtga tggcatatgt gacagagttt gtggacctgg 1260
gcaatgtctc agcgttgaga acattcagag ttctccgagc actgaaaaca atttcagtca 1320
ttccaggttt aaagaccatt gtgggggccc tgatccagtc ggtaaagaag ctttctgatg 1380
tgatgatcct gactgtgttc tgtctgagcg tgtttgctct cattgggctg cagctgttca 1440
tgggcaatct gaggaataaa tgtttgcagt ggcccccaag cgattctgct tttgaaacca 1500
acaccacttc ctactttaat ggcacaatgg attcaaatgg gacatttgtt aatgtaacaa 1560
tgagcacatt taactggaag gattacattg gagatgacag tcacttttat gttttggatg 1620
ggcaaaaaga ccctttactc tgtggaaatg gctcagatgc aggccagtgt ccagaaggat 1680
acatctgtgt gaaggctggt cgaaacccca actatggcta cacaagcttt gacaccttta 1740
gctgggcttt cctgtctcta tttcgactca tgactcaaga ctactgggaa aatctttacc 1800
agttgacatt acgtgctgct gggaaaacat acatgatatt ttttgtcctg gtcattttct 1860
tgggctcatt ttatttggtg aatttgatcc tggctgtggt ggccatggcc tatgaggggc 1920
agaatcaggc caccttggaa gaagcagaac aaaaagaggc cgaatttcag cagatgctcg 1980
aacagcttaa aaagcaacag gaagaagctc aggcagttgc ggcagcatca gctgcttcaa 2040
gagatttcag tggaataggt gggttaggag agctgttgga aagttcttca gaagcatcaa 2100
agttgagttc caaaagtgct aaagaatgga ggaaccgaag gaagaaaaga agacagagag 2160
agcaccttga aggaaacaac aaaggagaga gagacagctt tcccaaatcc gaatctgaag 2220
acagcgtcaa aagaagcagc ttccttttct ccatggatgg aaacagactg accagtgaca 2280
aaaaattctg ctcccctcat cagtctctct tgagtatccg tggctccctg ttttccccaa 2340
gacgcaatag caaaacaagc attttcagtt tcagaggtcg ggcaaaggat gttggatctg 2400
aaaatgactt tgctgatgat gaacacagca catttgaaga cagcgaaagc aggagagact 2460
cactgtttgt gccgcacaga catggagagc gacgcaacag taacggcacc accactgaaa 2520
cggaagtcag aaagagaagg ttaagctctt accagatttc aatggagatg ctggaggatt 2580
cctctggaag gcaaagagcc gtgagcatag ccagcattct gaccaacaca atggaagaac 2640
ttgaagaatc tagacagaaa tgtccgccat gctggtatag atttgccaat gtgttcttga 2700
tctgggactg ctgtgatgca tggttaaaag taaaacatct tgtgaattta attgttatgg 2760
atccatttgt tgatcttgcc atcactattt gcattgtctt aaatacccctc tttatggcca 2820
tggagcacta ccccatgact gagcaattca gtagtgtgtt gactgtagga aacctggtct 2880
ttactgggat ttttacagca gaaatggttc tcaagatcat tgccatggat ccttattact 2940
atttccaaga aggctggaat atctttgatg gaattattgt cagcctcagt ttaatggagc 3000
ttggtctgtc aaatgtggag ggattgtctg tactgcgatc attcagactg cttagagttt 3060
tcaagttggc aaaatcctgg cccacactaa atatgctaat taagatcatt ggcaattctg 3120
tgggggctct aggaaacctc accttggtgt tggccatcat cgtcttcatt tttgctgtgg 3180

tcggcatgca gctctttggt aagagctaca aagaatgtgt ctgcaagatc aatgatgact 3240
gtacgctccc acggtggcac atgaacgact tcttccactc cttcctgatt gtgttccgcg 3300
tgctgtgtgg agagtggata gagaccatgt gggactgtat ggaggtcgct ggccaaacca 3360
tgtgccttat tgttttcatg ttggtcatgg tcattggaaa ccttgtggtt ctgaacctct 3420
ttctggcctt attgttgagt tcatttagct cagacaacct tgctgctact gatgatgaca 3480
atgaaatgaa taatctgcag attgcagtag gaagaatgca aaagggaatt gattatgtga 3540
aaaataagat gcgggagtgt ttccaaaaag ccttttttag aaagccaaaa gttatagaaa 3600
tccatgaagg caataagata gacagctgca tgtccaatàa tactggaatt gaaataagca 3660
aagagcttaa ttatcttaga gatgggaatg gaaccaccag tggtgtaggt actggaagca 3720
gtgttgaaaa atacgtaatc gatgaaaatg attatatgtc attcataaac aaccccagcc 3780
tcaccgtcac agtgccaatt gctgttggag agtctgactt tgaaaactta aatactgaag 3840
agttcagcag tgagtcagaa ctagaagaaa gcaaggagaa attaaatgca accagctcat 3900
ctgaaggaag cacagttgat gttgttctac cccgagaagg tgaacaagct gaaactgaac 3960
ccgaagaaga ccttaaaccg gaagcttgtt ttactgaagg atgtattaaa aagtttccat 4020
tctgtcaagt aagtacagaa gaaggcaaag ggaagatctg gtggaatctt cgaaaaacct 4080
gctacagtat tgttgagcac aactggtttg agactttcat tgtgttcatg atccttctca 4140
gtagtggtgc attggccttt gaagatatat acattgaaca gcgaaagact atcaaaacca 4200
tgctagaata tgctgacaaa gtctttacct atatattcat tctggaaatg cttctcaaat 4260
gggttgctta tggatttcaa acatatttca ctaatgcctg gtgctggcta gatttcttga 4320
tcgttgatgt ttctttggtt agcctggtag ccaatgctct tggctactca gaactcggtg 4380
ccatcaaatc attacggaca ttaagagctt taagacctct aagagcctta tcccggtttg 4440
aaggcatgag ggtggttgtg aatgctcttg ttggagcaat tccctctatc atgaatgtgc 4500
tgttggtctg tctcatcttc tggttgatct ttagcatcat gggtgtgaat ttgtttgctg 4560
gcaagttcta ccactgtgtt aacatgacaa cgggtaacat gtttgacatt agtgatgtta 4620
acaatttgag tgactgtcag gctcttggca agcaagctcg gtggaaaaac gtgaaagtaa 4680
actttgataa tgttggcgct ggctatcttg cactgcttca agtggccaca tttaaaggct 4740
ggatggatat tatgtatgca gctgttgatt cacgagatgt taaacttcag cctgtatatg 4800
aagaaaatct gtacatgtat ttatactttg tcatctttat catctttggg tcattcttca 4860
ctctgaatct attcattggt gtcatcatag ataacttcaa ccagcagaaa aagaagtttg 4920
gaggtcaaga catctttatg acagaggaac agaaaaaata ttacaatgca atgaagaaac 4980
ttggatccaa gaaacctcag aaacccatac ctcgcccagc aaacaaattc caaggaatgg 5040
tctttgattt tgtaaccaga caagtctttg atatcagcat catgatcctc atctgcctca 5100
acatggtcac catgatggtg gaaacggatg accagggcaa atacatgacc ctagttttgt 5160
cccggatcaa cctagtgttc attgttctgt tcactggaga atttgtgctg aagctcgtct 5220
ccctcagaca ctactacttc actataggct ggaacatctt tgactttgtg gtggtgattc 5280
tctccattgt aggtatgttt ctggctgaga tgatagaaaa gtattttgtg tcccctacct 5340
tgttccgagt gatccgtctt gccaggattg gccgaatcct acgtctgatc aaaggagcaa 5400
aggggatccg cacgctgctc tttgctttga tgatgtccct tcctgcgttg tttaacatcg 5460
gcctcctgct cttcctggtc atgtttatct atgccatctt tgggatgtcc aactttgcct 5520
atgttaaaaa ggaagctgga attgatgaca tgttcaactt tgagaccttt ggcaacagca 5580
tgatctgctt gttccaaatt acaacctctg ctggatggga tggattgcta gcacctattc 5640
ttaatagtgc accacccgac tgtgaccctg acacaattca ccctggcagc tcagttaagg 5700
gagactgtgg gaacccatct gttgggattt tctttttttgt cagttacatc atcatatcct 5760
tcctggtggt ggtgaacagt tacatcgcgg tcatcctgga gaacttcagt gttgctactg 5820
aagaaagtgc agagcccctg agtgaggatg actttgagat gttctatgag gtttgggaaa 5880
agtttgatcc cgatgcgacc cagtttatag agttctctaa actctctgat tttgcagctg 5940
ccctggatcc tcctcttctc atagcaaaac ccaacaaagt ccagcttatt gccatggatc 6000
tgcccatggt cagtggtgac cggatccact gtcttgatat tttatttgcc tttacaaagc 6060

gtgttttggg tgagagtgga gagatggatg cccttcgaat acagatggaa gacaggttta 6120
tggcatcaaa cccctccaaa gtctcttatg agcctattac aaccactttg aaacgtaaac 6180
aagaggaggt gtctgccgct atcattcagc gtaatttcag atgttatctt ttaaagcaaa 6240
ggttaaaaaa tatatcaagt aactataaca aagaggcaat aaaggggagg attgacttac 6300
ctataaaaca agacatgatt attgacaaac tgaatgggaa ctccactcca gaaaaaacag 6360
atgggagttc ctctaccacc tctcctcctt cctatgatag tgtaacaaaa ccagacaagg 6420
aaaagtttga gaaagacaaa ccagaaaaag aaagcaaagg aaaagaggtc agagaaaatc 6480
aaaagtaaaa agaaacaaag aattatcttt gtgatcaatt gtttacagcc tatgaaggta 6540
aagtatatgt gtcaactgga cttcaagagg aggtccatgc caaactgact gttttaacaa 6600
atactcatag tcagtgccta tacaagacag tgaagtgacc tctctgtcac tgcaactctg 6660
tgaagcaggg tatcaacatt gacaagaggt tgctgttttt attaccagct gacactgctg 6720
aggagaaacc caatggctac ctagactata gggatagttg tgcaaagtga acattgtaac 6780
tacaccaaac acctttagta cagtccttgc atccattcta tttttaactt ccatatctgc 6840
catattttta caaaatttgt tctagtgcat ttccatggtc cccaattcat agtttattca 6900
taatgctatg tcactatttt tgtaaatgag gtttacgttg aagaaacagt atacaagaac 6960
cctgtctctc aaatgatcag acaaaggtgt tttgccagag agataaaatt tttgctcaaa 7020
accagaaaaa gaattgtaat ggctacagtt tcagttactt ccattttcta gatggcttta 7080
attttgaaag tattttagtc tgttatgttt gtttctatct gaacagttat gtgcctgtaa 7140
agtctcctct aatatttaaa ggattatttt tatgcaaagt attctgtttc agcaagtgca 7200
aattttattc taagtttcag agctctatat ttaatttagg tcaaatgctt tccaaaaagt 7260
aatctaataa atccattcta gaaaaatata tctaaagtat tgctttagaa tagttgttcc 7320
actttctgct gcagtattgc tttgccatct tctgctctca gcaaagctga tagtctatgt 7380
caattaaata ccctatgtta tgtaaatagt tattttatcc tgtggtgcat gtttgggcaa 7440
atatatatat agcctgataa acaacttcta ttaaatcaaa tatgtaccac agtgtatgtg 7500
tcttttgcaa gcttccaaca gggatgtatc ctgtatcatt cattaaacat agtttaaagg 7560
ctatcactaa tgcatgttaa tattgcctat gctgctctat tttactcaat ccattcttca 7620
caagtcttgg ttaaagaatg tcacatattg gtgatagaat gaattcaacc tgctctgtcc 7680
attatgtcaa gcagaataat ttgaagctat ttacaaacac ctttactttt gcacttttaa 7740
ttcaacatga gtatcatatg gtatctctct agatttcaag gaaacacact ggatactgcc 7800
tactgacaaa acctattctt catattttgc taaaaatatg tctaaaactt gcgcaaatat 7860
aaataatgta aaaatataat caactttatt tgtcagcatt ttgtacataa gaaaattatt 7920
ttcaggttga tgacatcaca atttatttta ctttatgctt ttgcttttga tttttaatca 7980
caattccaaa cttttgaatc cataagattt ttcaatggat aatttcctaa aataaaagtt 8040
agataatggg ttttatggat ttctttgtta taatatattt tctaccattc caataggaga 8100
tacattggtc aaacactcaa acctagatca ttttctacca actatggttg cctcaatata 8160
acctttttatt catagatgtt tttttttatt caacttttgt agtatttacg tatgcagact 8220
agtcttattt ttttaattcc tgctgcacta aagctattac aaatataaca tggactttgt 8280
tctttttagc catgaacaaa gtggcaaagt tgtgcaatta cctaacatga tataaatttt 8340
tgtttttttgc acaaaccaaa agtttaatgt taattctttt tacaaaacta tttactgtag 8400
tgtattgaag aactgcatgc agggaattgc tattgctaaa aagaatggtg agctacgtca 8460
ttattgagcc aaaagaataa atttcatttt ttattgcatt tcacttattg gcctctgggg 8520
ttttttgttt ttgtttttttg ctgttggcag tttaaaatat atataattaa taaaacctgt 8580
gcttgatctg acatttgtat acataaaagt ttacatgaat tttacaacag actagtgcat 8640
gattcaccaa gcagtactac agaacaaagg caaatgaaaa gcagctttgt gcacttttat 8700
gtgtgcaaag gatcaagttc acatgttcca actttcaggt ttgataataa tagtagtaac 8760
cacctacaat agctttcaat ttcaattaac tcccttggct ataagcatct aaactcatct 8820
tctttcaata taattgatgc tatctcctaa ttacttggtg gctaataaat gttacattct 8880
ttgttactta aatgcattat ataaactcct atgtatacat aaggtattaa tgatatagtt 8940

attgagaatt tatattaact ttttttcaa gaacccttgg atttatgtga ggtcaaaacc 9000
aaactcttat tctcagtgga aaactccagt tgtaatgcat atttttaaag acaatttgga 9060
tctaaatatg tatttcataa ttctcccata ataaattata taaggtggct aa 9112

<210> 66
<211> 9112
<212> DNA
<213> Homo sapiens

<400> 66
accatagagt gaatctcaga acaggaagcg gaggcataag cagagaggat tctggaaagg 60
tctctttgtt ttcttatcca cagagaaaga aagaaaaaaa attgtaacta atttgtaaac 120
ctctgtggtc aaaaaaaaaa aaaaaaaaaa aagctgaaca gctgcagagg aagacacgtt 180
ataccctaac catcttggat gctgggcttt gttatgctgt aattcataag gctctgtttt 240
atcagagatt atggagcaag aaaactgaag ccaagccaca tcaaggtttg acagggatga 300
gatacctgtc aaggattcat agtagagtgg cttactggga aaggagcaaa gaatctcttc 360
tagggatatt gtaagaataa atgagataat tcacagaagg gacctggagc ttttccggaa 420
aaaggtgctg tgactatcta aggggaaaag ctgagagtct ggaactagcc tatcttccga 480
ggacttagag acaacagtat gggaatttca acgagacgtt tttactttct tttgaccaag 540
attcaaattc tttattccag cccttgataa gtaaataaga aggtaattcg tatgcaagaa 600
gctacacgta attaaatgtg caggatgaaa agatggcaca ggcactgttg gtacccccag 660
gacctgaaag cttccgcctt tttactagag aatctcttgc tgctatcgaa aaacgtgctg 720
cagaagagaa agccaagaag cccaaaaagg aacaagataa tgatgatgag aacaaaccaa 780
agccaaatag tgacttggaa gctggaaaga accttccatt tatttatgga gacattcctc 840
cagagatggt gtcagagccc ctggaggacc tggatcccta ctatatcaat aagaaaactt 900
ttatagtaat gaataaagga aaggcaattt cccgattcag tgccacctct gccttgtata 960
ttttaactcc actaaaccct gttaggaaaa ttgctabsaa gattttggta cattctttat 1020
tcagcatgct tatcatgtgc actattttga ccaactgtgt atttatgacc ttgagcaacc 1080
ctcctgactg gacaaagaat gtagagtaca cattcactgg aatctatacc tttgagtcac 1140
ttataaaaat cttggcaaga gggttttgct tagaagattt tacgtttctt cgtgatccat 1200
ggaactggct ggatttcagt gtcattgtga tggcgtatgt aacagaattt gtaagcctag 1260
gcaatgtttc agcccttcga actttcagag tcttgagagc tctgaaaact atttctgtaa 1320
tcccaggttt aaagaccatt gtgggggccc tgatccagtc ggtaaagaag ctttctgatg 1380
tgatgatcct gactgtgttc tgtctgagcg tgtttgctct cattgggctg cagctgttca 1440
tgggcaatct gaggaataaa tgtttgcagt ggcccccaag cgattctgct tttgaaacca 1500
acaccacttc ctactttaat ggcacaatgg attcaaatgg gacatttgtt aatgtaacaa 1560
tgagcacatt taactggaag gattacattg gagatgacag tcacttttat gttttggatg 1620
ggcaaaaaga ccctttactc tgtggaaatg gctcagatgc aggccagtgt ccagaaggat 1680
acatctgtgt gaaggctggt cgaaacccca actatggcta cacaagcttt gacaccttta 1740
gctgggcttt cctgtctcta tttcgactca tgactcaaga ctactgggaa aatctttacc 1800
agttgacatt acgtgctgct gggaaaacat acatgatatt ttttgtcctg gtcatttttct 1860
tgggctcatt ttatttggtg aatttgatcc tggctgtggt ggccatggcc tatgaggggc 1920
agaatcaggc caccttggaa gaagcagaac aaaaagaggc cgaatttcag cagatgctcg 1980
aacagcttaa aaagcaacag gaagaagctc aggcagttgc ggcagcatca gctgcttcaa 2040
gagatttcag tggaataggt gggttaggag agctgttgga aagttcttca gaagcatcaa 2100
agttgagttc caaaagtgct aaagaatgga ggaaccgaag gaagaaaaga agacagagag 2160
agcaccttga aggaaacaac aaaggagaga gagacagctt tcccaaatcc gaatctgaag 2220

acagcgtcaa aagaagcagc ttccttttct ccatggatgg aaacagactg accagtgaca 2280
aaaaattctg ctcccctcat cagtctctct tgagtatccg tggctccctg ttttccccaa 2340
gacgcaatag caaaacaagc attttcagtt tcagaggtcg ggcaaaggat gttggatctg 2400
aaaatgactt tgctgatgat gaacacagca catttgaaga cagcgaaagc aggagagact 2460
cactgtttgt gccgcacaga catggagagc gacgcaacag taacggcacc accactgaaa 2520
cggaagtcag aaagagaagg ttaagctctt accagatttc aatggagatg ctggaggatt 2580
cctctggaag gcaaagagcc gtgagcatag ccagcattct gaccaacaca atggaagaac 2640
ttgaagaatc tagacagaaa tgtccgccat gctggtatag atttgccaat gtgttcttga 2700
tctgggactg ctgtgatgca tggttaaaag taaaacatct tgtgaattta attgttatgg 2760
atccatttgt tgatcttgcc atcactattt gcattgtctt aaatacccctc tttatggcca 2820
tggagcacta ccccatgact gagcaattca gtagtgtgtt gactgtagga aacctggtct 2880
ttactgggat ttttacagca gaaatggttc tcaagatcat tgccatggat ccttattact 2940
atttccaaga aggctggaat atctttgatg gaattattgt cagcctcagt ttaatggagc 3000
ttggtctgtc aaatgtggag ggattgtctg tactgcgatc attcagactg cttagagttt 3060
tcaagttggc aaaatcctgg cccacactaa atatgctaat taagatcatt ggcaattctg 3120
tgggggctct aggaaacctc accttggtgt tggccatcat cgtcttcatt tttgctgtgg 3180
tcggcatgca gctctttggt aagagctaca aagaatgtgt ctgcaagatc aatgatgact 3240
gtacgctccc acggtggcac atgaacgact tcttccactc cttcctgatt gtgttccgcg 3300
tgctgtgtgg agagtggata gagaccatgt gggactgtat ggaggtcgct ggccaaacca 3360
tgtgccttat tgttttcatg ttggtcatgg tcattggaaa ccttgtggtt ctgaacctct 3420
ttctggcctt attgttgagt tcatttagct cagacaacct tgctgctact gatgatgaca 3480
atgaaatgaa taatctgcag attgcagtag gaagaatgca aaagggaatt gattatgtga 3540
aaaataagat gcgggagtgt ttccaaaaag ccttttttag aaagccaaaa gttatagaaa 3600
tccatgaagg caataagata gacagctgca tgtccaataa tactggaatt gaaataagca 3660
aagagcttaa ttatcttaga gatgggaatg gaaccaccag tggtgtaggt actggaagca 3720
gtgttgaaaa atacgtaatc gatgaaaatg attatatgtc attcataaac aaccccagcc 3780
tcaccgtcac agtgccaatt gctgttggag agtctgactt tgaaaactta aatactgaag 3840
agttcagcag tgagtcagaa ctagaagaaa gcaaggagaa attaaatgca accagctcat 3900
ctgaaggaag cacagttgat gttgttctac cccgagaagg tgaacaagct gaaactgaac 3960
ccgaagaaga ccttaaaccg gaagcttgtt ttactgaagg atgtattaaa aagtttccat 4020
tctgtcaagt aagtacagaa gaaggcaaag ggaagatctg gtggaatctt cgaaaaacct 4080
gctacagtat tgttgagcac aactggtttg agactttcat tgtgttcatg atccttctca 4140
gtagtggtgc attggccttt gaagatatat acattgaaca gcgaaagact atcaaaacca 4200
tgctagaata tgctgacaaa gtctttacct atatattcat tctggaaatg cttctcaaat 4260
gggttgctta tggatttcaa acatatttca ctaatgcctg gtgctggcta gatttcttga 4320
tcgttgatgt ttctttggtt agcctggtag ccaatgctct tggctactca gaactcggtg 4380
ccatcaaatc attacggaca ttaagagctt taagacctct aagagcctta tcccggtttg 4440
aaggcatgag ggtggttgtg aatgctcttg ttggagcaat tccctctatc atgaatgtgc 4500
tgttggtctg tctcatcttc tggttgatct ttagcatcat gggtgtgaat ttgtttgctg 4560
gcaagttcta ccactgtgtt aacatgacaa cgggtaacat gtttgacatt agtgatgtta 4620
acaatttgag tgactgtcag gctcttggca agcaagctcg gtggaaaaac gtgaaagtaa 4680
actttgataa tgttggcgct ggctatcttg cactgcttca agtggccaca tttaaaggct 4740
ggatggatat tatgtatgca gctgttgatt cacgagatgt taaacttcag cctgtatatg 4800
aagaaaatct gtacatgtat ttatactttg tcatctttat catctttggg tcattcttca 4860
ctctgaatct attcattggt gtcatcatag ataacttcaa ccagcagaaa aagaagtttg 4920
gaggtcaaga catctttatg acagaggaac agaaaaaata ttacaatgca atgaagaaac 4980
ttggatccaa gaaacctcag aaacccatac ctcgcccagc aaacaaattc caaggaatgg 5040
tctttgattt tgtaaccaga caagtctttg atatcagcat catgatcctc atctgcctca 5100

acatggtcac catgatggtg gaaacggatg accagggcaa atacatgacc ctagttttgt 5160
cccggatcaa cctagtgttc attgttctgt tcactggaga atttgtgctg aagctcgtct 5220
ccctcagaca ctactacttc actataggct ggaacatctt tgactttgtg gtggtgattc 5280
tctccattgt aggtatgttt ctggctgaga tgatagaaaa gtattttgtg tcccctacct 5340
tgttccgagt gatccgtctt gccaggattg gccgaatcct acgtctgatc aaaggagcaa 5400
aggggatccg cacgctgctc tttgctttga tgatgtccct tcctgcgttg tttaacatcg 5460
gcctcctgct cttcctggtc atgtttatct atgccatctt tgggatgtcc aactttgcct 5520
atgttaaaaa ggaagctgga attgatgaca tgttcaactt tgagaccttt ggcaacagca 5580
tgatctgctt gttccaaatt acaacctctg ctggatggga tggattgcta gcacctattc 5640
ttaatagtgc accacccgac tgtgaccctg acacaattca ccctggcagc tcagttaagg 5700
gagactgtgg gaacccatct gttgggattt tctttttttgt cagttacatc atcatatcct 5760
tcctggtggt ggtgaacagt tacatcgcgg tcatcctgga gaacttcagt gttgctactg 5820
aagaaagtgc agagcccctg agtgaggatg actttgagat gttctatgag gtttgggaaa 5880
agtttgatcc cgatgcgacc cagtttatag agttctctaa actctctgat tttgcagctg 5940
ccctggatcc tcctcttctc atagcaaaac ccaacaaagt ccagcttatt gccatggatc 6000
tgcccatggt cagtggtgac cggatccact gtcttgatat tttatttgcc tttacaaagc 6060
gtgttttggg tgagagtgga gagatggatg cccttcgaat acagatggaa gacaggttta 6120
tggcatcaaa ccccctccaaa gtctcttatg agcctattac aaccactttg aaacgtaaac 6180
aagaggaggt gtctgccgct atcattcagc gtaatttcag atgttatctt ttaaagcaaa 6240
ggttaaaaaa tatatcaagt aactataaca aagaggcaat aaaggggagg attgacttac 6300
ctataaaaca agacatgatt attgacaaac tgaatgggaa ctccactcca gaaaaaacag 6360
atgggagttc ctctaccacc tctcctcctt cctatgatag tgtaacaaaa ccagacaagg 6420
aaaagtttga gaaagacaaa ccagaaaaag aaagcaaagg aaaagaggtc agagaaaatc 6480
aaaagtaaaa agaaacaaag aattatcttt gtgatcaatt gtttacagcc tatgaaggta 6540
aagtatatgt gtcaactgga cttcaagagg aggtccatgc caaactgact gttttaacaa 6600
atactcatag tcagtgccta tacaagacag tgaagtgacc tctctgtcac tgcaactctg 6660
tgaagcaggg tatcaacatt gacaagaggt tgctgttttt attaccagct gacactgctg 6720
aggagaaacc caatggctac ctagactata gggatagttg tgcaaagtga acattgtaac 6780
tacaccaaac acctttagta cagtccttgc atccattcta tttttaactt ccatatctgc 6840
catatttta caaaatttgt tctagtgcat ttccatggtc cccaattcat agtttattca 6900
taatgctatg tcactatttt tgtaaatgag gtttacgttg aagaaacagt atacaagaac 6960
cctgtctctc aaatgatcag acaaaggtgt tttgccagag agataaaatt tttgctcaaa 7020
accagaaaaa gaattgtaat ggctacagtt tcagttactt ccattttcta gatggcttta 7080
attttgaaag tattttagtc tgttatgttt gtttctatct gaacagttat gtgcctgtaa 7140
agtctcctct aatatttaaa ggattatttt tatgcaaagt attctgtttc agcaagtgca 7200
aattttattc taagtttcag agctctatat ttaatttagg tcaaatgctt tccaaaaagt 7260
aatctaataa atccattcta gaaaaatata tctaaagtat tgctttagaa tagttgttcc 7320
actttctgct gcagtattgc tttgccatct tctgctctca gcaaagctga tagtctatgt 7380
caattaaata ccctatgtta tgtaaatagt tattttatcc tgtggtgcat gtttgggcaa 7440
atatatatat agcctgataa acaacttcta ttaaatcaaa tatgtaccac agtgtatgtg 7500
tcttttgcaa gcttccaaca gggatgtatc ctgtatcatt cattaaacat agtttaaagg 7560
ctatcactaa tgcatgttaa tattgcctat gctgctctat tttactcaat ccattcttca 7620
caagtcttgg ttaaagaatg tcacatattg gtgatagaat gaattcaacc tgctctgtcc 7680
attatgtcaa gcagaataat ttgaagctat ttacaaacac ctttactttt gcacttttaa 7740
ttcaacatga gtatcatatg gtatctctct agatttcaag gaaacacact ggatactgcc 7800
tactgacaaa acctattctt catattttgc taaaaatatg tctaaaactt gcgcaaatat 7860
aaataatgta aaaatataat caactttatt tgtcagcatt ttgtacataa gaaaattatt 7920
ttcaggttga tgacatcaca atttatttta ctttatgctt ttgcttttga tttttaatca 7980

caattccaaa cttttgaatc cataagattt ttcaatggat aatttcctaa aataaaagtt 8040
agataatggg ttttatggat ttctttgtta taatatattt tctaccattc caataggaga 8100
tacattggtc aaacactcaa acctagatca ttttctacca actatggttg cctcaatata 8160
acctttttatt catagatgtt tttttttatt caacttttgt agtatttacg tatgcagact 8220
agtcttattt ttttaattcc tgctgcacta aagctattac aaatataaca tggactttgt 8280
tctttttagc catgaacaaa gtggcaaagt tgtgcaatta cctaacatga tataaatttt 8340
tgttttttgc acaaaccaaa agtttaatgt taattctttt tacaaaacta tttactgtag 8400
tgtattgaag aactgcatgc agggaattgc tattgctaaa aagaatggtg agctacgtca 8460
ttattgagcc aaaagaataa atttcatttt ttattgcatt tcacttattg gcctctgggg 8520
ttttttgttt ttgtttttttg ctgttggcag tttaaaatat atataattaa taaaacctgt 8580
gcttgatctg acatttgtat acataaaagt ttacatgaat tttacaacag actagtgcat 8640
gattcaccaa gcagtactac agaacaaagg caaatgaaaa gcagctttgt gcacttttat 8700
gtgtgcaaag gatcaagttc acatgttcca actttcaggt ttgataataa tagtagtaac 8760
cacctacaat agctttcaat ttcaattaac tcccttggct ataagcatct aaactcatct 8820
tctttcaata taattgatgc tatctcctaa ttacttggtg gctaataaat gttacattct 8880
ttgttactta aatgcattat ataaactcct atgtatacat aaggtattaa tgatatagtt 8940
attgagaatt tatattaact ttttttttcaa gaacccttgg atttatgtga ggtcaaaacc 9000
aaactcttat tctcagtgga aaactccagt tgtaatgcat atttttaaag acaatttgga 9060
tctaaatatg tatttcataa ttctcccata ataaattata taaggtggct aa 9112

<210> 67
<211> 1951
<212> PRT
<213> Homo sapiens

<400> 67

```
Met Ala Gln Ala Leu Leu Val Pro Pro Gly Pro Glu Ser Phe Arg Leu
  1               5                  10                  15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Ala Ala Glu Glu
             20                  25                  30

Lys Ala Lys Lys Pro Lys Lys Glu Gln Asp Asn Asp Asp Glu Asn Lys
         35                  40                  45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
     50                  55                  60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
 65                  70                  75                  80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Met Asn Lys Gly
                85                  90                  95

Lys Ala Ile Ser Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
            100                 105                 110
```

Pro Leu Asn Pro Val Arg Lys Ile Ala Xaa Lys Ile Leu Val His Ser
115 120 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
130 135 140

Met Thr Leu Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
145 150 155 160

Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala Arg
165 170 175

Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
180 185 190

Leu Asp Phe Ser Val Ile Val Met Ala Tyr Val Thr Glu Phe Val Asp
195 200 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
210 215 220

Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
225 230 235 240

Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
245 250 255

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
260 265 270

Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Ser Asp Ser Ala Phe Glu
275 280 285

Thr Asn Thr Thr Ser Tyr Phe Asn Gly Thr Met Asp Ser Asn Gly Thr
290 295 300

Phe Val Asn Val Thr Met Ser Thr Phe Asn Trp Lys Asp Tyr Ile Gly
305 310 315 320

Asp Asp Ser His Phe Tyr Val Leu Asp Gly Gln Lys Asp Pro Leu Leu
325 330 335

Cys Gly Asn Gly Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile Cys
340 345 350

Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr
355 360 365

```
Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Tyr
    370                 375                 380

Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr
385                 390                 395                 400

Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val
                405                 410                 415

Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Gly Gln Asn Gln
            420                 425                 430

Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met
        435                 440                 445

Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Val Ala Ala
    450                 455                 460

Ala Ser Ala Ala Ser Arg Asp Phe Ser Gly Ile Gly Gly Leu Gly Glu
465                 470                 475                 480

Leu Leu Glu Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala
                485                 490                 495

Lys Glu Trp Arg Asn Arg Arg Lys Lys Arg Arg Gln Arg Glu His Leu
            500                 505                 510

Glu Gly Asn Asn Lys Gly Glu Arg Asp Ser Phe Pro Lys Ser Glu Ser
        515                 520                 525

Glu Asp Ser Val Lys Arg Ser Ser Phe Leu Phe Ser Met Asp Gly Asn
    530                 535                 540

Arg Leu Thr Ser Asp Lys Lys Phe Cys Ser Pro His Gln Ser Leu Leu
545                 550                 555                 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Lys Thr Ser
                565                 570                 575

Ile Phe Ser Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp
            580                 585                 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Ser Glu Ser Arg Arg
        595                 600                 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg Asn Ser Asn
    610                 615                 620
```

Gly Thr Thr Thr Glu Thr Glu Val Arg Lys Arg Arg Leu Ser Ser Tyr
625 630 635 640

Gln Ile Ser Met Glu Met Leu Glu Asp Ser Ser Gly Arg Gln Arg Ala
645 650 655

Val Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
660 665 670

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Arg Phe Ala Asn Val Phe
675 680 685

Leu Ile Trp Asp Cys Cys Asp Ala Trp Leu Lys Val Lys His Leu Val
690 695 700

Asn Leu Ile Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
705 710 715 720

Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
725 730 735

Glu Gln Phe Ser Ser Val Leu Thr Val Gly Asn Leu Val Phe Thr Gly
740 745 750

Ile Phe Thr Ala Glu Met Val Leu Lys Ile Ile Ala Met Asp Pro Tyr
755 760 765

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Ile Ile Val Ser
770 775 780

Leu Ser Leu Met Glu Leu Gly Leu Ser Asn Val Glu Gly Leu Ser Val
785 790 795 800

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
805 810 815

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
820 825 830

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
835 840 845

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
850 855 860

Lys Ile Asn Asp Asp Cys Thr Leu Pro Arg Trp His Met Asn Asp Phe
865 870 875 880

```
Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
                885                 890                 895

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
            900                 905                 910

Ile Val Phe Met Leu Val Met Val Ile Gly Asn Leu Val Val Leu Asn
        915                 920                 925

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
    930                 935                 940

Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
945                 950                 955                 960

Arg Met Gln Lys Gly Ile Asp Tyr Val Lys Asn Lys Met Arg Glu Cys
                965                 970                 975

Phe Gln Lys Ala Phe Phe Arg Lys Pro Lys Val Ile Glu Ile His Glu
            980                 985                 990

Gly Asn Lys Ile Asp Ser Cys Met Ser Asn Asn Thr Gly Ile Glu Ile
        995                1000                1005

Ser Lys Glu Leu Asn Tyr Leu Arg Asp Gly Asn Gly Thr Thr Ser Gly
   1010                1015                1020

Val Gly Thr Gly Ser Ser Val Glu Lys Tyr Val Ile Asp Glu Asn Asp
1025                1030                1035                1040

Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile
                1045                1050                1055

Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser
            1060                1065                1070

Ser Glu Ser Glu Leu Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser
        1075                1080                1085

Ser Ser Glu Gly Ser Thr Val Asp Val Val Leu Pro Arg Glu Gly Glu
   1090                1095                1100

Gln Ala Glu Thr Glu Pro Glu Glu Asp Leu Lys Pro Glu Ala Cys Phe
1105                1110                1115                1120

Thr Glu Gly Cys Ile Lys Lys Phe Pro Phe Cys Gln Val Ser Thr Glu
                1125                1130                1135
```

Glu Gly Lys Gly Lys Ile Trp Trp Asn Leu Arg Lys Thr Cys Tyr Ser
1140 1145 1150

Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu
1155 1160 1165

Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu Gln Arg
1170 1175 1180

Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr
1185 1190 1195 1200

Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Phe Gln
1205 1210 1215

Thr Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp
1220 1225 1230

Val Ser Leu Val Ser Leu Val Ala Asn Ala Leu Gly Tyr Ser Glu Leu
1235 1240 1245

Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro Leu Arg
1250 1255 1260

Ala Leu Ser Arg Phe Glu Gly Met Arg Val Val Val Asn Ala Leu Val
1265 1270 1275 1280

Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe
1285 1290 1295

Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe
1300 1305 1310

Tyr His Cys Val Asn Met Thr Thr Gly Asn Met Phe Asp Ile Ser Asp
1315 1320 1325

Val Asn Asn Leu Ser Asp Cys Gln Ala Leu Gly Lys Gln Ala Arg Trp
1330 1335 1340

Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu Ala
1345 1350 1355 1360

Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala
1365 1370 1375

Ala Val Asp Ser Arg Asp Val Lys Leu Gln Pro Val Tyr Glu Glu Asn
1380 1385 1390

Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
1395 1400 1405

Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln
1410 1415 1420

Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
1425 1430 1435 1440

Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
1445 1450 1455

Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe Gln Gly Met Val Phe Asp
1460 1465 1470

Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
1475 1480 1485

Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Gly Lys Tyr
1490 1495 1500

Met Thr Leu Val Leu Ser Arg Ile Asn Leu Val Phe Ile Val Leu Phe
1505 1510 1515 1520

Thr Gly Glu Phe Val Leu Lys Leu Val Ser Leu Arg His Tyr Tyr Phe
1525 1530 1535

Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile
1540 1545 1550

Val Gly Met Phe Leu Ala Glu Met Ile Glu Lys Tyr Phe Val Ser Pro
1555 1560 1565

Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
1570 1575 1580

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
1585 1590 1595 1600

Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val
1605 1610 1615

Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys
1620 1625 1630

Lys Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn
1635 1640 1645

Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
1650 1655 1660

Leu Leu Ala Pro Ile Leu Asn Ser Ala Pro Pro Asp Cys Asp Pro Asp
1665 1670 1675 1680

Thr Ile His Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
1685 1690 1695

Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
1700 1705 1710

Val Val Asn Ser Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala
1715 1720 1725

Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe
1730 1735 1740

Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu
1745 1750 1755 1760

Phe Ser Lys Leu Ser Asp Phe Ala Ala Ala Leu Asp Pro Pro Leu Leu
1765 1770 1775

Ile Ala Lys Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met
1780 1785 1790

Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr
1795 1800 1805

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
1810 1815 1820

Met Glu Asp Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Glu
1825 1830 1835 1840

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Ala
1845 1850 1855

Ile Ile Gln Arg Asn Phe Arg Cys Tyr Leu Leu Lys Gln Arg Leu Lys
1860 1865 1870

Asn Ile Ser Ser Asn Tyr Asn Lys Glu Ala Ile Lys Gly Arg Ile Asp
1875 1880 1885

Leu Pro Ile Lys Gln Asp Met Ile Ile Asp Lys Leu Asn Gly Asn Ser
1890 1895 1900

```
Thr Pro Glu Lys Thr Asp Gly Ser Ser Ser Thr Thr Ser Pro Pro Ser
1905                1910                1915                1920

Tyr Asp Ser Val Thr Lys Pro Asp Lys Glu Lys Phe Glu Lys Asp Lys
                1925                1930                1935

Pro Glu Lys Glu Ser Lys Gly Lys Glu Val Arg Glu Asn Gln Lys
            1940                1945                1950
```

<210> 68
<211> 1951
<212> PRT
<213> Homo sapiens

<400> 68

```
Met Ala Gln Ala Leu Leu Val Pro Pro Gly Pro Glu Ser Phe Arg Leu
  1               5                  10                  15

Phe Thr Arg Glu Ser Leu Ala Ala Ile Glu Lys Arg Ala Ala Glu Glu
             20                  25                  30

Lys Ala Lys Lys Pro Lys Lys Glu Gln Asp Asn Asp Asp Glu Asn Lys
         35                  40                  45

Pro Lys Pro Asn Ser Asp Leu Glu Ala Gly Lys Asn Leu Pro Phe Ile
     50                  55                  60

Tyr Gly Asp Ile Pro Pro Glu Met Val Ser Glu Pro Leu Glu Asp Leu
 65                  70                  75                  80

Asp Pro Tyr Tyr Ile Asn Lys Lys Thr Phe Ile Val Met Asn Lys Gly
                 85                  90                  95

Lys Ala Ile Ser Arg Phe Ser Ala Thr Ser Ala Leu Tyr Ile Leu Thr
            100                 105                 110

Pro Leu Asn Pro Val Arg Lys Ile Ala Xaa Lys Ile Leu Val His Ser
        115                 120                 125

Leu Phe Ser Met Leu Ile Met Cys Thr Ile Leu Thr Asn Cys Val Phe
    130                 135                 140

Met Thr Leu Ser Asn Pro Pro Asp Trp Thr Lys Asn Val Glu Tyr Thr
145                 150                 155                 160

Phe Thr Gly Ile Tyr Thr Phe Glu Ser Leu Ile Lys Ile Leu Ala Arg
                165                 170                 175
```

Gly Phe Cys Leu Glu Asp Phe Thr Phe Leu Arg Asp Pro Trp Asn Trp
180 185 190

Leu Asp Phe Ser Val Ile Val Met Ala Tyr Val Thr Glu Phe Val Ser
195 200 205

Leu Gly Asn Val Ser Ala Leu Arg Thr Phe Arg Val Leu Arg Ala Leu
210 215 220

Lys Thr Ile Ser Val Ile Pro Gly Leu Lys Thr Ile Val Gly Ala Leu
225 230 235 240

Ile Gln Ser Val Lys Lys Leu Ser Asp Val Met Ile Leu Thr Val Phe
245 250 255

Cys Leu Ser Val Phe Ala Leu Ile Gly Leu Gln Leu Phe Met Gly Asn
260 265 270

Leu Arg Asn Lys Cys Leu Gln Trp Pro Pro Ser Asp Ser Ala Phe Glu
275 280 285

Thr Asn Thr Thr Ser Tyr Phe Asn Gly Thr Met Asp Ser Asn Gly Thr
290 295 300

Phe Val Asn Val Thr Met Ser Thr Phe Asn Trp Lys Asp Tyr Ile Gly
305 310 315 320

Asp Asp Ser His Phe Tyr Val Leu Asp Gly Gln Lys Asp Pro Leu Leu
325 330 335

Cys Gly Asn Gly Ser Asp Ala Gly Gln Cys Pro Glu Gly Tyr Ile Cys
340 345 350

Val Lys Ala Gly Arg Asn Pro Asn Tyr Gly Tyr Thr Ser Phe Asp Thr
355 360 365

Phe Ser Trp Ala Phe Leu Ser Leu Phe Arg Leu Met Thr Gln Asp Tyr
370 375 380

Trp Glu Asn Leu Tyr Gln Leu Thr Leu Arg Ala Ala Gly Lys Thr Tyr
385 390 395 400

Met Ile Phe Phe Val Leu Val Ile Phe Leu Gly Ser Phe Tyr Leu Val
405 410 415

Asn Leu Ile Leu Ala Val Val Ala Met Ala Tyr Glu Gly Gln Asn Gln
420 425 430

```
Ala Thr Leu Glu Glu Ala Glu Gln Lys Glu Ala Glu Phe Gln Gln Met
        435                 440                 445

Leu Glu Gln Leu Lys Lys Gln Gln Glu Glu Ala Gln Ala Val Ala Ala
    450                 455                 460

Ala Ser Ala Ala Ser Arg Asp Phe Ser Gly Ile Gly Gly Leu Gly Glu
465                 470                 475                 480

Leu Leu Glu Ser Ser Ser Glu Ala Ser Lys Leu Ser Ser Lys Ser Ala
                485                 490                 495

Lys Glu Trp Arg Asn Arg Arg Lys Lys Arg Arg Gln Arg Glu His Leu
            500                 505                 510

Glu Gly Asn Asn Lys Gly Glu Arg Asp Ser Phe Pro Lys Ser Glu Ser
        515                 520                 525

Glu Asp Ser Val Lys Arg Ser Ser Phe Leu Phe Ser Met Asp Gly Asn
    530                 535                 540

Arg Leu Thr Ser Asp Lys Lys Phe Cys Ser Pro His Gln Ser Leu Leu
545                 550                 555                 560

Ser Ile Arg Gly Ser Leu Phe Ser Pro Arg Arg Asn Ser Lys Thr Ser
                565                 570                 575

Ile Phe Ser Phe Arg Gly Arg Ala Lys Asp Val Gly Ser Glu Asn Asp
            580                 585                 590

Phe Ala Asp Asp Glu His Ser Thr Phe Glu Asp Ser Glu Ser Arg Arg
        595                 600                 605

Asp Ser Leu Phe Val Pro His Arg His Gly Glu Arg Arg Asn Ser Asn
    610                 615                 620

Gly Thr Thr Thr Glu Thr Glu Val Arg Lys Arg Arg Leu Ser Ser Tyr
625                 630                 635                 640

Gln Ile Ser Met Glu Met Leu Glu Asp Ser Ser Gly Arg Gln Arg Ala
                645                 650                 655

Val Ser Ile Ala Ser Ile Leu Thr Asn Thr Met Glu Glu Leu Glu Glu
            660                 665                 670

Ser Arg Gln Lys Cys Pro Pro Cys Trp Tyr Arg Phe Ala Asn Val Phe
        675                 680                 685
```

```
Leu Ile Trp Asp Cys Cys Asp Ala Trp Leu Lys Val Lys His Leu Val
    690                 695                 700

Asn Leu Ile Val Met Asp Pro Phe Val Asp Leu Ala Ile Thr Ile Cys
705                 710                 715                 720

Ile Val Leu Asn Thr Leu Phe Met Ala Met Glu His Tyr Pro Met Thr
                725                 730                 735

Glu Gln Phe Ser Ser Val Leu Thr Val Gly Asn Leu Val Phe Thr Gly
            740                 745                 750

Ile Phe Thr Ala Glu Met Val Leu Lys Ile Ile Ala Met Asp Pro Tyr
        755                 760                 765

Tyr Tyr Phe Gln Glu Gly Trp Asn Ile Phe Asp Gly Ile Ile Val Ser
    770                 775                 780

Leu Ser Leu Met Glu Leu Gly Leu Ser Asn Val Glu Gly Leu Ser Val
785                 790                 795                 800

Leu Arg Ser Phe Arg Leu Leu Arg Val Phe Lys Leu Ala Lys Ser Trp
                805                 810                 815

Pro Thr Leu Asn Met Leu Ile Lys Ile Ile Gly Asn Ser Val Gly Ala
            820                 825                 830

Leu Gly Asn Leu Thr Leu Val Leu Ala Ile Ile Val Phe Ile Phe Ala
        835                 840                 845

Val Val Gly Met Gln Leu Phe Gly Lys Ser Tyr Lys Glu Cys Val Cys
    850                 855                 860

Lys Ile Asn Asp Asp Cys Thr Leu Pro Arg Trp His Met Asn Asp Phe
865                 870                 875                 880

Phe His Ser Phe Leu Ile Val Phe Arg Val Leu Cys Gly Glu Trp Ile
                885                 890                 895

Glu Thr Met Trp Asp Cys Met Glu Val Ala Gly Gln Thr Met Cys Leu
            900                 905                 910

Ile Val Phe Met Leu Val Met Val Ile Gly Asn Leu Val Val Leu Asn
        915                 920                 925

Leu Phe Leu Ala Leu Leu Leu Ser Ser Phe Ser Ser Asp Asn Leu Ala
    930                 935                 940
```

```
Ala Thr Asp Asp Asp Asn Glu Met Asn Asn Leu Gln Ile Ala Val Gly
945                 950                 955                 960

Arg Met Gln Lys Gly Ile Asp Tyr Val Lys Asn Lys Met Arg Glu Cys
                965                 970                 975

Phe Gln Lys Ala Phe Phe Arg Lys Pro Lys Val Ile Glu Ile His Glu
            980                 985                 990

Gly Asn Lys Ile Asp Ser Cys Met Ser Asn Asn Thr Gly Ile Glu Ile
        995                1000                1005

Ser Lys Glu Leu Asn Tyr Leu Arg Asp Gly Asn Gly Thr Thr Ser Gly
   1010                1015                1020

Val Gly Thr Gly Ser Ser Val Glu Lys Tyr Val Ile Asp Glu Asn Asp
1025                1030                1035                1040

Tyr Met Ser Phe Ile Asn Asn Pro Ser Leu Thr Val Thr Val Pro Ile
                1045                1050                1055

Ala Val Gly Glu Ser Asp Phe Glu Asn Leu Asn Thr Glu Glu Phe Ser
            1060                1065                1070

Ser Glu Ser Glu Leu Glu Glu Ser Lys Glu Lys Leu Asn Ala Thr Ser
        1075                1080                1085

Ser Ser Glu Gly Ser Thr Val Asp Val Val Leu Pro Arg Glu Gly Glu
   1090                1095                1100

Gln Ala Glu Thr Glu Pro Glu Glu Asp Leu Lys Pro Glu Ala Cys Phe
1105                1110                1115                1120

Thr Glu Gly Cys Ile Lys Lys Phe Pro Phe Cys Gln Val Ser Thr Glu
                1125                1130                1135

Glu Gly Lys Gly Lys Ile Trp Trp Asn Leu Arg Lys Thr Cys Tyr Ser
            1140                1145                1150

Ile Val Glu His Asn Trp Phe Glu Thr Phe Ile Val Phe Met Ile Leu
        1155                1160                1165

Leu Ser Ser Gly Ala Leu Ala Phe Glu Asp Ile Tyr Ile Glu Gln Arg
   1170                1175                1180

Lys Thr Ile Lys Thr Met Leu Glu Tyr Ala Asp Lys Val Phe Thr Tyr
1185                1190                1195                1200
```

Ile Phe Ile Leu Glu Met Leu Leu Lys Trp Val Ala Tyr Gly Phe Gln
1205 1210 1215

Thr Tyr Phe Thr Asn Ala Trp Cys Trp Leu Asp Phe Leu Ile Val Asp
1220 1225 1230

Val Ser Leu Val Ser Leu Val Ala Asn Ala Leu Gly Tyr Ser Glu Leu
1235 1240 1245

Gly Ala Ile Lys Ser Leu Arg Thr Leu Arg Ala Leu Arg Pro Leu Arg
1250 1255 1260

Ala Leu Ser Arg Phe Glu Gly Met Arg Val Val Val Asn Ala Leu Val
1265 1270 1275 1280

Gly Ala Ile Pro Ser Ile Met Asn Val Leu Leu Val Cys Leu Ile Phe
1285 1290 1295

Trp Leu Ile Phe Ser Ile Met Gly Val Asn Leu Phe Ala Gly Lys Phe
1300 1305 1310

Tyr His Cys Val Asn Met Thr Thr Gly Asn Met Phe Asp Ile Ser Asp
1315 1320 1325

Val Asn Asn Leu Ser Asp Cys Gln Ala Leu Gly Lys Gln Ala Arg Trp
1330 1335 1340

Lys Asn Val Lys Val Asn Phe Asp Asn Val Gly Ala Gly Tyr Leu Ala
1345 1350 1355 1360

Leu Leu Gln Val Ala Thr Phe Lys Gly Trp Met Asp Ile Met Tyr Ala
1365 1370 1375

Ala Val Asp Ser Arg Asp Val Lys Leu Gln Pro Val Tyr Glu Glu Asn
1380 1385 1390

Leu Tyr Met Tyr Leu Tyr Phe Val Ile Phe Ile Ile Phe Gly Ser Phe
1395 1400 1405

Phe Thr Leu Asn Leu Phe Ile Gly Val Ile Ile Asp Asn Phe Asn Gln
1410 1415 1420

Gln Lys Lys Lys Phe Gly Gly Gln Asp Ile Phe Met Thr Glu Glu Gln
1425 1430 1435 1440

Lys Lys Tyr Tyr Asn Ala Met Lys Lys Leu Gly Ser Lys Lys Pro Gln
1445 1450 1455

Lys Pro Ile Pro Arg Pro Ala Asn Lys Phe Gln Gly Met Val Phe Asp
1460 1465 1470

Phe Val Thr Arg Gln Val Phe Asp Ile Ser Ile Met Ile Leu Ile Cys
1475 1480 1485

Leu Asn Met Val Thr Met Met Val Glu Thr Asp Asp Gln Gly Lys Tyr
1490 1495 1500

Met Thr Leu Val Leu Ser Arg Ile Asn Leu Val Phe Ile Val Leu Phe
1505 1510 1515 1520

Thr Gly Glu Phe Val Leu Lys Leu Val Ser Leu Arg His Tyr Tyr Phe
1525 1530 1535

Thr Ile Gly Trp Asn Ile Phe Asp Phe Val Val Val Ile Leu Ser Ile
1540 1545 1550

Val Gly Met Phe Leu Ala Glu Met Ile Glu Lys Tyr Phe Val Ser Pro
1555 1560 1565

Thr Leu Phe Arg Val Ile Arg Leu Ala Arg Ile Gly Arg Ile Leu Arg
1570 1575 1580

Leu Ile Lys Gly Ala Lys Gly Ile Arg Thr Leu Leu Phe Ala Leu Met
1585 1590 1595 1600

Met Ser Leu Pro Ala Leu Phe Asn Ile Gly Leu Leu Leu Phe Leu Val
1605 1610 1615

Met Phe Ile Tyr Ala Ile Phe Gly Met Ser Asn Phe Ala Tyr Val Lys
1620 1625 1630

Lys Glu Ala Gly Ile Asp Asp Met Phe Asn Phe Glu Thr Phe Gly Asn
1635 1640 1645

Ser Met Ile Cys Leu Phe Gln Ile Thr Thr Ser Ala Gly Trp Asp Gly
1650 1655 1660

Leu Leu Ala Pro Ile Leu Asn Ser Ala Pro Pro Asp Cys Asp Pro Asp
1665 1670 1675 1680

Thr Ile His Pro Gly Ser Ser Val Lys Gly Asp Cys Gly Asn Pro Ser
1685 1690 1695

Val Gly Ile Phe Phe Phe Val Ser Tyr Ile Ile Ile Ser Phe Leu Val
1700 1705 1710

```
Val Val Asn Ser Tyr Ile Ala Val Ile Leu Glu Asn Phe Ser Val Ala
       1715                1720                1725

Thr Glu Glu Ser Ala Glu Pro Leu Ser Glu Asp Asp Phe Glu Met Phe
   1730                1735                1740

Tyr Glu Val Trp Glu Lys Phe Asp Pro Asp Ala Thr Gln Phe Ile Glu
1745                1750                1755                1760

Phe Ser Lys Leu Ser Asp Phe Ala Ala Ala Leu Asp Pro Pro Leu Leu
               1765                1770                1775

Ile Ala Lys Pro Asn Lys Val Gln Leu Ile Ala Met Asp Leu Pro Met
           1780                1785                1790

Val Ser Gly Asp Arg Ile His Cys Leu Asp Ile Leu Phe Ala Phe Thr
       1795                1800                1805

Lys Arg Val Leu Gly Glu Ser Gly Glu Met Asp Ala Leu Arg Ile Gln
   1810                1815                1820

Met Glu Asp Arg Phe Met Ala Ser Asn Pro Ser Lys Val Ser Tyr Glu
1825                1830                1835                1840

Pro Ile Thr Thr Thr Leu Lys Arg Lys Gln Glu Glu Val Ser Ala Ala
               1845                1850                1855

Ile Ile Gln Arg Asn Phe Arg Cys Tyr Leu Leu Lys Gln Arg Leu Lys
           1860                1865                1870

Asn Ile Ser Ser Asn Tyr Asn Lys Glu Ala Ile Lys Gly Arg Ile Asp
       1875                1880                1885

Leu Pro Ile Lys Gln Asp Met Ile Ile Asp Lys Leu Asn Gly Asn Ser
   1890                1895                1900

Thr Pro Glu Lys Thr Asp Gly Ser Ser Ser Thr Thr Ser Pro Pro Ser
1905                1910                1915                1920

Tyr Asp Ser Val Thr Lys Pro Asp Lys Glu Lys Phe Glu Lys Asp Lys
               1925                1930                1935

Pro Glu Lys Glu Ser Lys Gly Lys Glu Val Arg Glu Asn Gln Lys
           1940                1945                1950
```

<210> 69

<211> 1380
<212> DNA
<213> Homo sapiens

<400> 69
aatgtattta tttaattgat gataaactgt aataaaatca tagttgtttg ctctaaagta 60
gatatgaaag gtcagatgaa acaataacat acatctggat tgagaaatat cttaataact 120
gatggattat ttttattttc tttatgtatt gtgtgcttca atatcctaat aaataatatt 180
agctaggttc actgatgtat agaatctttt tctacattta gatatttctt gcaaatgttt 240
taccagaaag caacacaaaa atactatcag tgagtatgtg tttacactgt tctctaagga 300
gtcaaattcc tcaccttgaa aataattcat cccaggaaga gaaaaggttt tcaaaagact 360
agagcaggcc acaagggagc tttcgcaaaa ctctacacgt aaagggtaat gtaaacttaa 420
aacctatttt tcaaacagta atttatatat cttttaattt tagtagttta tgtgtgaaac 480
aatcatgcaa aacaacaaag tgataaaatt ttttaaaaaa attagtgaga tgcaaataac 540
tgaatatgta aaaggtctca tacatattta tatgtagtag ataagttaca ttttttttagt 600
gtgttgggaa attttagctc acatcacctc tctactgtca tcttggggca ctttcatgac 660
tacccatgct tcatgcaggt ttactttcct ccctgtgaca gaggataatg ggaatgtttt 720
ttctttggct caattttgtg tgtgtccgcc agtagatggc gtaccacttt gagtgcgatc 780
ggccttttttt tctttctttt tttttttcct caaagctgtt ttctgatata tgttgggtac 840
catagagtga atctcagaac aggaagcgga ggcataagca gagaggattc tggaaaggtc 900
tctttgtttt cttatccaca gagaaagaaa gaaaaaaaat tgtaactaat ttgtaaacct 960
ctgtggtcaa aaaaaaaaaa aaaaaaaaaa gctgaacagc tgcagaggaa gacacgttat 1020
accctaacca tcttggatgc tgggctttgt tatgctgtaa ttcataaggc tctgttttat 1080
caggtaagct gacaaaacat ttcattatct gcaccataga acctagctac caggtcattt 1140
tccttacttt aaaatcatct tcatgctgct atttttaacc cagtgttgtt taaatgtaaa 1200
ttacaggaac caaaggcatc gtttgatgtg taaactgctt actatttctt tatctttcaa 1260
agaaaataga gcctgtctgg aaatggtgat ttatggtaca tactaggcat caatggtctt 1320
gtgtttttgt agatgcttat gattaattgt attcagaaaa aatatttttt attatactta 1380

<210> 70
<211> 840
<212> DNA
<213> Homo sapiens

<400> 70
agggaagaac agaaggatgc tcaggagtgc cagcatgcct tcagaaagac taaatggatc 60
aaggctgcca aagaaggggg agcacccctg tcccaaccct aggatcctgg cagtggttcc 120
tggtcccatt cttcctaaat catgctaggg catgctttta acaagggtca aatatcttgc 180
tttgcatcat ccttgctttc tcgatccagg gccataaaaa aaaaaggaat aaaacccaga 240
cacagagcca gagcacccct atgccaaatg tcaaagatta taggctaatt tcacctgtat 300
tctctttcta cagagattat ggagcaagaa aactgaagcc aagccacatc aaggtttgac 360
agggatgaga tacctgtcaa ggattcatag tagagtggct tactgggaaa ggagcaaaga 420
atctcttcta gggatattgt aagaataaat gagataattc acagaaggga cctggagctt 480
ttccggaaaa aggtgctgtg actatctaag gtaactaaac aacttctggg tataagtttg 540
tttttgtgga aaataaacta aaatctctac tatttaacaa ggacagctgt atcaggacca 600
aaagaaggca gaggggtgtt ttcttccttc ctctaccagt ttgttcttcc aaagaggcaa 660
atacatacag ggagacatag cacagatgac cttagggaat ggaatgatgc caaaggctgt 720

tgatgtaaga aagagagatt aactcagttt ttttttttgtt tttgtttttt tgttgttgtt 780
gttgttgttt tgagacagag tctctctctg tcgcccaggc tggagtgcag tggcatgaac 840

<210> 71
<211> 780
<212> DNA
<213> Homo sapiens

<400> 71
gatatattaa attttatgta ttttaataaa ttataatgtg catataatca ttaataatat 60
atatattcca caccaaggca tcagtaagaa ttaatttta aagtctgctc taatgtgaat 120
ataaaattat gtaagaactc tgtataataa gctcacagag tacaagaaag gagaggaaaa 180
aagtaaaaga gaactgcgaa agaactatga gggatttcca aacagcaaaa ttgtcattga 240
agccatgaga aactctactc actaaattct ttaatttctc agcctaccca aatattgggc 300
aaaccctaat tctcttgcag gggaaaagct gagagtctgg aactagccta tcttccgagg 360
acttagagac aacagtatgg gaatttcaac gagacgtttt tactttcttt tgaccaagat 420
tcaaattctt tattccagcc cttgataagt aaataagaag gtaaaggact atttatttgt 480
aaaaagtttt tcatgatttt gtgatggcac cttgttccat atcatctcag ataaatcaga 540
ataatttgtg aaaattactc ggtgatttcc acattagata ttttaaacct aatgttattt 600
ctaaaacaaa aaccaaccag gagaatccaa ttaagtaaaa tgtatgtatt aatataaatt 660
agctattccc atctggaaaa gggcagccat ttctgtgttg aggtgcctca atgatactga 720
ggctgagaca ggttagatga tacaggcata ccattagcag cagactcaat actaacccag 780

<210> 72
<211> 1025
<212> DNA
<213> Homo sapiens

<400> 72
acaaagttat gaaaaggcgg ggggcaggat gcagaataat taagcaattt tattgacaaa 60
ctthactggc attactcttt tgctgaaagt atactatatt ttggcttaca gtgtcaaaac 120
agaatttttt aaatgctttt aaaaaatgga caaaattata gatattcttg agtttaaata 180
taatgtttat atattatata tactgtacat tgtagaatgg ctaaatcaaa ctaattaaca 240
ttaagtacag acttttgata gatttatgaa cttggcttat tgagaatgag gttgaatgat 300
gatgttttca agttcaaatg tgtagtgcag tactaaaagc atgacttaat gtttatagct 360
ttaaaaagtt actaaagaat gacattttgg ttgatgttct tatgcccaat cgcttgcttt 420
cctaactctt gtgcaatttt tctttttatt gcaggtaatt cgtatgcaag aagctacacg 480
taattaaatg tgcaggatga aaagatggca caggcactgt tggtaccccc aggacctgaa 540
agcttccgcc tttttactag agaatctctt gctgctatcg aaaaacgtgc tgcagaagag 600
aaagccaaga agcccaaaaa ggaacaagat aatgatgatg agaacaaacc aaagccaaat 660
agtgacttgg aagctggaaa gaaccttcca tttatttatg gagacattcc tccagagatg 720
gtgtcagagc ccctggagga cctggatccc tactatatca ataagaaagt gagtattgat 780
tttagacttc taataaatct ttaatgaaac tcttaactgt aatatacttt tctgggcctt 840
atatacagca tcacaatttt tcttctgtta aagattttat aatactcttc actgtcactt 900
atttttatca caatataata aaacaaacat ttataagaaa tgaagtcaag agttggttac 960
agtcaggaaa tatgaataga tgaatgattt ctacaatttc acagtgataa ttcagatagt 1020

caaaa 1025

<210> 73
<211> 433
<212> DNA
<213> Homo sapiens

<400> 73
tgtaacyata tgttaattta aacatctaac atgtttgtag ttatgatata tcaactggtt 60
taaacaaacc agtttgaaca aacaaattcy atttttaaa aaggtcctca tgtatgtaag 120
ctccttaaat aagcccatgt ctaatttagt aattttactc gtattttctg tttcagactt 180
ttatagtaat gaataaagga aaggcaattt cccgattcag tgccacctct gccttgtata 240
ttttaactcc actaaaccct gttaggaaaa ttgctabsaa gattttggta cattcatatc 300
cttttaatgt gaattgccta aatgctattt ctaacagttg attttaaaga aaatgtcagt 360
tatattttca agtatctgta aaatttcttt gagattaatg gtaacattgt tagtttaatt 420
catttatttg cat 433

<210> 74
<211> 450
<212> DNA
<213> Homo sapiens

<400> 74
gagtgcacca aggccatatc acaggctttg aagtttctta ttattttatc attgttttaa 60
aacaaataat attaatttca cagtttttgc atcgataaac ttttttgtgt gttttggatc 120
atttataaat ggccatggta acctactaac atttattcct taactataat ctactttatt 180
cagcatgctt atcatgtgca ctattttgac caactgtgta tttatgacct tgagcaaccc 240
tcctgactgg acaaagaatg tagagtaagt aggaataact tctgggaatg agaaatgcac 300
actcaaattc tctagcaatc tccttgtggg tatagcctga cttatggttt ccacttctgt 360
ctaagaaaag ttattttcat aatatgcagc cggtaaggga ggtctttcgg gggagctatt 420
cttctacgag gtaagtattt tcccacaaaa 450

<210> 75
<211> 701
<212> DNA
<213> Homo sapiens

<400> 75
aaaatttacc atttgyggct ttccattaca tttctatcag ataactctgc gctagtaggt 60
caaactagat gattatccat aagatacatg aaactattat tctaaaaccc aaatagttaa 120
accagattag attcctaaag aatatatttt ctcttcagtt taactctttg ctcaggcttg 180
taaaactaac taaatgaata gattatttgg taaatagaag taaggaacaa tattttaatg 240
aattgaaaaa ccacaaaagg ataggatttg ctatgattga aaacatttat tttaacagtt 300
caagcaaaat tgttaatttt ggcttggatg tttttcctag gtacacattc actggaatct 360
ataccttga gtcacttata aaaatcttgg caagagggtt ttgcttagaa gattttacgt 420

ttcttcgtga tccatggaac tggctggatt tcagtgtcat tgtgatggcg tgagtaactt 480
tgaaaatttg ataagcgcaa aggagtgaaa atagtcatag tacaaacaag gtctttgtgt 540
catatattaa atgtagagct ttcttgttag tcaagttaac tatatgggtt gtgtattttc 600
agaatacata ttagaataca tattgcaatg taaatatatc cagtaaatga tcaataaatg 660
gggttatctt catgtcatat agtctttctc ttcatcaaaa t 701

<210> 76
<211> 286
<212> DNA
<213> Homo sapiens

<400> 76
atttgttaaa ctcacagggc tctatgtgcc aaacccagca ttaagtcctt atttagtata 60
aactttgcca aaactatcag taactctgat ttaattctgc aggtatgtaa cagaatttgt 120
aagcctaggc aatgtttcag cccttcgaac tttcagagtc ttgagagctc tgaaaactat 180
ttctgtaatc ccaggtaaga agaaactggt gtaaggtagt aggcccctta tatctccaac 240
ttttcttgtg tgttattgtg tttgtgtgtg aactccccta ttacag 286

<210> 77
<211> 515
<212> DNA
<213> Homo sapiens

<400> 77
gtaagaagaa actggtgtaa ggtagtaggc cccttatatc tccaactttt cttgtgtgtt 60
attgtgtttg tgtgtgaact cccctattac agatatgtga cagagtttgt ggacctgggc 120
aatgtctcag cgttgagaac attcagagtt ctccgagcac tgaaaacaat ttcagtcatt 180
ccaggtgaga gctaggttaa acaccgaggt tgactttaat tattgagttt gaaatcaatt 240
tatatgactt acagcattag ccttgttgct tattattaca gttcatcccg gtaaataatg 300
ccaaatgatg tttcaatgtc agtttagctc ctaaaatttt ataaattaca tgcgtattta 360
taaagtcagc ctttgagttt aacagaaaat tgcatgagac atcttcaaaa aatgctaatt 420
tgggcctctt gcgctctctc tctctctttt tcactaccat ggctttacta acagatttgg 480
attttaccat tcgctgcaga tgtagttcaa aaatg 515

<210> 78
<211> 564
<212> DNA
<213> Homo sapiens

<400> 78
aaacttcctg actagatatt taaaccttca tattgaattt ccagcaagca cactgttcat 60
gtgtaaaatc tgctgttcat ctatttccca aatcatcagg ctatccatac agctttggtg 120
tctaaatagt caagcaatca tttatggggg aaagagaatg tgtgtgacta ttaagaaatc 180
atgatttctg gcactcttcc tcaggtaacc tatagttctc tctctgcagg tttaaagacc 240
attgtggggg ccctgatcca gtcggtaaag aagctttctg atgtgatgat cctgactgtg 300

ttctgtctga gcgtgtttgc tctcattggg ctgcagctgt tcatgggcaa tctgaggaat 360
aaatgtttgc agtggccccc aagcgattct gcttttgaaa ccaacaccac ttcctacttt 420
aatggcacaa tggattcaaa tgggacattt gttaatgtaa caatgagcac atttaactgg 480
aaggataaca ttggagatga cagtaagaag tattacatta tgttaacctt agtgttgctg 540
aatgaatttt caactataaa tagt 564

<210> 79
<211> 497
<212> DNA
<213> Homo sapiens

<400> 79
tgagactgtg ggtgtacagc cacctttgta aataactgaa atagtccaac tctgatttat 60
tactaatact aatgtgaata ggattaatat gaaataaaat gggtttttt ttgtattaac 120
aggtcacttt tatgttttgg atgggcaaaa agacccttta ctctgtggaa atggttcaga 180
tgcagggtaa gaaacataat atatattttt aagatataga actctttgcg aaaaaaaaaa 240
gtaggtagga aaacaactac atggttatat gtgtagcctt accatgtatg caataaagag 300
cagtgctgct cccctaggaa gtgccttgtc tgccttaccg gattgccact ggtcctaaac 360
tcacagcaat taaaaattat ccctttgtga agacctttcc ccaaaatttc acagttaaga 420
tgttcttaaa ttgatgctcc aatgtgtgaa ggcccagagt ctgtctttgc tgtacatcta 480
tcagagctgt taggaaa 497

<210> 80
<211> 501
<212> DNA
<213> Homo sapiens

<400> 80
aaagagtaaa aatatggtaa ggtcagagcc aaaagtgtgt ggttgctagc tttctgccat 60
tctaaatgtc trwaaawatt tatttgcatc taaattttct atcggtcttc ctagtgaatt 120
tcatctgata agtttcacgg tgggcaatca cctaaagtgt tctggaaatt aaagcaagat 180
aattcgtcac agatagcagc tttgggtttt gaaaattcct ataagtcaaa taaattgaaa 240
ttgctgtaat ttctaaactg accctacctc catttctctc tcttatagcc agtgtccaga 300
aggatacatc tgtgtgaagg ctggtcgaaa ccccaactat ggctacacaa gctttgacac 360
ctttagctgg gctttcctgt ctctatttcg actcatgact caagactact gggaaaatct 420
ttaccagttg gtaaggtcca aatgagcatg cataacattt atttttatag acatgtatga 480
aatgaaaagc ataggctgag t 501

<210> 81
<211> 432
<212> DNA
<213> Homo sapiens

<400> 81
agctaattag tctactgact atctaactgt ggtaatcaga tatttatttg gggacattat 60

actaaaatac tgatggaatt atcccccatt tcccctagac attacgtgct gctgggaaaa 120
catacatgat attttttgtc ctggtcattt tcttgggctc attttatttg gtgaatttga 180
tcctggctgt ggtggccatg gcctatgagg ggcagaatca ggccaccttg gaagaagcag 240
aacaaaaaga ggccgaattt cagcagatgc tcgaacagct taaaaagcaa caggaagaag 300
ctcaggtact gagtgataaa mgcaaagatt tatcattatt attmttagtt tctaagtaga 360
aatagtgtta tactatagag ggtagattgg aactgctttt tcattttata tatmggcatt 420
gtcattagac ac 432

<210> 82
<211> 489
<212> DNA
<213> Homo sapiens

<400> 82
tgcaaactgt tttcaaagct ctgtgttcta aatagtgcct ggctttgttt tatgacaggc 60
agttgcggca gcatcagctg cttcaagaga tttcagtgga ataggtgggt taggagagct 120
gttggaaagt tcttcagaag catcaaagtt gagttccaaa agtgctaaag aatggaggaa 180
ccgaaggaag aaaagaagac agagagagca ccttgaagga aacaacaaag gagagagaga 240
cagctttccc aaatccgaat ctgaagacag cgtcaaaaga agcagcttcc ttttctccat 300
ggatggaaac agactgacca gtgacaaaaa attctgctcc cctcatcagg tatgattttc 360
tactaagtgc tctggtttct ttgtcattgc tattgctttt tagtttttgt attttgtttt 420
ggtacacttt tgtactatct gtacttcagt tgagggacag ggaactaaca tttaatatag 480
ttgtttaaa 489

<210> 83
<211> 653
<212> DNA
<213> Homo sapiens

<400> 83
gtgaagacta aatgaagtgg ttgtatactt agtaaattgc aaatcagtat tgttagtcag 60
aaaaacactc tttgtactta aatttgcttt aataaaaata tcaaaatata tgtgtcctct 120
ataaatttga ttatccatgt ttaagggcaa gagtatacta actccaaaga aaacagatcc 180
tttaatatta atatttatta aataattgcg ttcttcccct acccccatcc cattcctttc 240
ctttttgctt tctctgcagt ctctcttgag tatccgtggc tccctgtttt ccccaagacg 300
caatagcaaa acaagcattt tcagtttcag aggtcgggca aaggatgttg gatctgaaaa 360
tgactttgct gatgatgaac acagcacatt tgaagacagc gaaagcagga gagactcact 420
gtttgtgccg cacagacatg gagagcgacg caacagtaac gttagtcagg ccagtatgtc 480
atccaggatg gtgccagggc ttccagcaaa tggggaagat gcacagcact gtggattgca 540
atggtgtggt ttccttggtg ggtggacctt cagctctaac gtcacctact gggcaacttc 600
cccagaggtg ataatagatg acctagctgc tactgacatt attcaccaat ttg 653

<210> 84
<211> 566
<212> DNA

<213> Homo sapiens

<400> 84
gaattctctt aaaggtacta cctgtgatac ttttttaaa aaaaaactgt ttataactta 60
gcaataattc aatattttat tcttgaaatt cttacctgga aaattgcatg tagcatgatt 120
tgcaaagaaa tgctatgtgg tgttgtatta cttattggga agagtggttt gagccatcag 180
tatttggttt gcagggcacc accactgaaa cggaagtcag aaagagaagg ttaagctctt 240
accagatttc aatggagatg ctggaggatt cctctggaag gcaaagagcc gtgagcatag 300
ccagcattct gaccaacaca atggaaggta agagcaggtc atggaacagc caactttctg 360
tgattatgtg ctttgtgaac tattccttct tttcatagaa ttactgaagt ctgttaccca 420
gatcgaacta tatattagac ctaagaatgt gatatatggt gtacattatc acattgntta 480
caaaactaat attggcctta ttctttttga cttgggtcct taccttactt gcagagtgat 540
atttcaacac ttgatattat atcaat 566

<210> 85
<211> 748
<212> DNA
<213> Homo sapiens

<400> 85
tagtcatttt aaaagcaaaa tattaaattc aaagtgctta ttttctgtat tcaaaagaga 60
aaaaagtcga tctatatgac attttaatta acattttctg aaaatattta atgggattgt 120
cttctcaagt ttcttaagta atatgaactt ctattttcaa atataagcat caattttgtt 180
aaataatgta aaatctacta gcaataataa ctcatttttg ttgttattta ctactcttcc 240
ttgttattgt ccctccagaa cttgaagaat ctagacagaa atgtccgcca tgctggtata 300
gatttgccaa tgtgttcttg atctgggact gctgtgatgc atggttaaaa gtaaaacatc 360
ttgtgaattt aattgttatg gatccatttg ttgatcttgc catcactatt tgcattgtct 420
taaataccct ctttatggcc atggagcact accccatgac tgagcaattc agtagtgtgt 480
tgactgtagg aaacctggta agtacatttg aagtttactt atttactttg gtagatgtgg 540
gagagataga ccaaagggaa agatgtattt gtgctgtgtt gaacccaaaa attatatcct 600
ctttcctcat agaaagaaat atctaaggaa tattacaggg aatctcagag atacagccta 660
aaactcaact ggtatgaatg ctgattgttt aggccaatgt ctgtgctgat tgatcatggt 720
gtcttaccag ttgtaaacgt ctcaaaat 748

<210> 86
<211> 664
<212> DNA
<213> Homo sapiens

<400> 86
ctaagacttg aattgatttg tcactattct ctcactttaa attttagata tttttattcc 60
tgtctaatgt tcttctttat aaattcgtgt agcatcagtg ttttcagtgc tcttgatagt 120
agtgctgatc tctaattttt taggtcttta ctgggatttt tacagcagaa atggttctca 180
agatcattgc catggatcct tattactatt tccaagaagg ctggaatatc tttgatggaa 240
ttattgtcag cctcagttta atggagcttg gtctgtcaaa tgtggaggga ttgtctgtac 300
tgcgatcatt cagactggta tctatttata tatatccctg tcgctcattg gcacaacatt 360

tattttgaaa ttgaatcaat gtatatttat ataattatta attttaattt taaatttaca 420
tcaatatgtg acattctaag aaaacatgta aacatccyct ttaaagctaa accattttct 480
aagaatgatg aaagcattca aaatactcta taatgattag gtatgtaggg cacattagaa 540
aacctacaag tactttctaa aactgtgttt taagtttatg aagctttttt ggccttacag 600
tctgtaaaga tacgcaaata aaaatttaga ccccagttaa ttttagcttt ttattaaccc 660
tact 664

<210> 87
<211> 750
<212> DNA
<213> Homo sapiens

<400> 87
tatttttatt tttgcactta aatgatatta tgaccagatt tacaattcta atattgttaa 60
cactattttt tctggatttg aaattgaatc agttcagtat attttgagtt tttacatcta 120
ccacgtgtgg ttctatgata ccacatacta ataaaataat gtctaaaatt atattatgat 180
tactactaac agcatctttt cacttgatta cagcttagag ttttcaagtt ggcaaaatcc 240
tggcccacac taaatatgct aattaagatc attggcaatt ctgtgggggc tctaggaaac 300
ctcaccttgg tgttggccat catcgtcttc atttttgctg tggtcggcat gcagctcttt 360
ggtaagagct acaaagaatg tgtctgcaag atcaatgatg actgtacgct cccacggtgg 420
cacatgaacg acttcttcca ctccttcctg attgtgttcc gcgtgctgtg tggagagtgg 480
atagagacca tgtgggactg tatggaggtc gctggccaaa ccatgtgcct tattgttttc 540
atgttggtca tggtcattgg aaaccttgtg gtatgtatgt agtacaaatg ctcataaatt 600
agaacaagag cagacagtag ctaggaacgt ggccagatgt agtaaacata tctctggttt 660
atagtaagtg gcctagactg aaatcccccc attagcactc agagaataag caagttattt 720
aacttctcct gggctctggt ttcccatttt 750

<210> 88
<211> 768
<212> DNA
<213> Homo sapiens

<400> 88
ccttagagca ggatattagg tcctttaaag agtgtgtgac ttagacatgg catctgaaat 60
atagtaagca ttcaataaac atttgttgaa ataattttag caaagatcta tgagttccct 120
ttttaggctg ttatttaaat gcatatttca atattaarat aggcattttt ctttttttct 180
tttaggttct gaacctcttt ctggccttat tgttgagttc atttagctca gacaaccttg 240
ctgctactga tgatgacaat gaaatgaata atctgcagat tgcagtagga agaatgcaaa 300
agggaattga ttatgtgaaa aataagatgc gggagtgttt ccaaaaagcc ttttttagaa 360
agccaaaagt tatagaaatc catgaaggca ataagataga cagctgcatg tccaataata 420
ctggaattga aataagcaaa gagcttaatt atcttagaga tgggaatgga accaccagtg 480
gtgtaggtac tggaagcagt gttgaaaaat acgtaatcga tgaaaatgat tatatgtcat 540
tcataaacaa ccccagcctc accgtcacag tgccaattgc tgttggagag tctgactttg 600
aaaacttaaa tactgaagag ttcagcagtg agtcagaact agaagaaagc aaggaggtaa 660
ggaatgcttt taaatttttt gttccatttc ctatgataac catgtactac agttatttac 720
tattttcatt gtgcttatat gcattatcga aaagcaatga ttgtaagt 768

<210> 89
<211> 471
<212> DNA
<213> Homo sapiens

<400> 89
taattattag tacataatga tcagtaatgc taatagagtt aaatgctatc actacatttt 60
ttttcacaca atgacacagt atttcccagt tagttaaata aaaggggaa aatcacatct 120
ttgaaatggg attttgtttc cagaaattaa atgcaaccag ctcatctgaa ggaagcacag 180
ttgatgttgt tctaccccga gaaggtgaac aagctgaaac tgaacccgaa gaagacctta 240
aaccggaagc ttgttttact gaaggtaaac aagctctgat gtgattaaat acaatctccc 300
cttgttcttt acggagactg aatatgcctc atttaaaaaa aaaaatttag caaacgaggt 360
gtggtggctt atgcctgtaa ccccaaaatt ttgggaggct acggtaggag gattgcttga 420
ccccaggagt ttgagaccac cctgggaaat gtagtaaggc tttgcctcta c 471

<210> 90
<211> 623
<212> DNA
<213> Homo sapiens

<400> 90
gaattctaag tagctggctg agtatataag tctgagaata attcattata caggagggat 60
gctgacgata actaggaaat gaaggagatg gttaccctat gaaatgatta cctggaagtg 120
gagtggggaa ggggcaagaa agtttatttt ttcctattta agattaaaat atatttttta 180
attaactata tttsattttt aggatgtatt aaaaagtttc cattctgtca agtaagtaca 240
gaagaaggca aagggaagat ctggtggaat cttcgaaaaa cctgctacag tattgttgag 300
cacaactggt ttgagacttt cattgtgttc atgatccttc tcagtagtgg tgcattggta 360
agtgaaatgc atattggcaa gaatcagatt ctggtgaaat agtttattct ccaaaattac 420
cagatgcaaa cactgagctt cagaatcaaa agaaaaggca tatctgtgtc ttgcagagct 480
tggcacccaa ggtttaacga tgcaaaattc agttctgaac aaatcagcac catgaaacag 540
ccagatggaa tttctcatct ggtgtttatc taacagatgt tttcctcact gagacaacca 600
tttgcagaga cattctgtaa cca 623

<210> 91
<211> 520
<212> DNA
<213> Homo sapiens

<400> 91
ctagttagtc tttagatttg tctcatgttc aatgtttatg taaaatatca ataatcaaaa 60
ttattctttt gtactcacta ttatactaag caatttttc aaatatttag aagaagcaag 120
ccatttaagt aaaataaaat atttttgatt cataggcctt tgaagatata tacattgaac 180
agcgaaagac tatcaaaacc atgctagaat atgctgacaa agtctttacc tatatattca 240
ttctggaaat gcttctcaaa tgggttgctt atggatttca aacatatttc actaatgcct 300

ggtgctggct agatttcttg atcgttgatg taagtatttt aagtgatttt tataaaattg 360
tttttaaaag aggcaagttt gacatttcat atgtttctgt tattaaaact ttcactaata 420
atgacataat tatgcagtta tttaaacaaa actgtaacat atgcaacaat gaggaatatc 480
tcatgggaaa gagtagagga ggtcctaaac atgggcagtg 520

<210> 92
<211> 595
<212> DNA
<213> Homo sapiens

<400> 92
ctaactaata atttaagcac acatccatga aggatctggc attgaactca atcctgaatt 60
atcagtggta tatgcacaag ttgaaaaggg gtccatggta taaaatatct aactggagat 120
attgacacgt gttgataaat atgggcaagt attctggttt cattggttaa aaaaaagcaa 180
tagtatgaga tgagactggc aatataagat gaccccacta tgtggaagat gaaagttgcc 240
aaggtatgtc caaattagta tttagtctgc attaaataga taccacaccc tataccttca 300
gtcaacagtt tatttcttgg tgaactaatt aatttttttt tccttttgta ggtttctttg 360
gttagcctgg tagccaatgc tcttggctac tcagaactcg gtgccatcaa atcattacgg 420
acattaagag ctttaagacc tctaagagcc ttatcccggt ttgaaggcat gagggtaaga 480
agaatagaca ctctaattat tcatgtcaaa aattacatgt aggtaatgat ttagatagaa 540
aagggtgcca tactcttctg atatttattt caatagaaat tacagaatta gaagc 595

<210> 93
<211> 787
<212> DNA
<213> Homo sapiens

<400> 93
ccagcataca aacattttct gactccatct tactatacca ggtttttaat gatttctttt 60
catactgtag catattttgc tttccttaaa accttagctc tttagttgtg tcattgtttg 120
ttttccttca aatatgtgct agaaaaatta gaagaaacaa cttgtccacc tagattttta 180
tttaactctt ttcaagcaca tattaatact aaacaaatac attgaaggaa tggtttccat 240
tcaaaaggtt tgtaagctat gttcccctcg ctgtctcttc taggtggttg tgaatgctct 300
tgttggagca attccctcta tcatgaatgt gctgttggtc tgtctcatct tctggttgat 360
ctttagcatc atgggtgtga atttgtttgc tggcaagttc taccactgtg ttaacatgac 420
aacgggtaac atgtttgaca ttagtgatgt taacaatttg agtgactgtc aggctcttgg 480
caagcaagct cggtggaaaa acgtgaaagt aaactttgat aatgttggcg ctggctatct 540
tgcactgctt caagtggtaa gtggctactg tacgagtttt gaaaaagttt tcaagatgtt 600
tcaaggaaga ttatttccct gatgttcttc gtttgaatga ctaacatttg acagcatgaa 660
aaaaagttaa tgataacacc tataatatca gcttgaattg atcataaaaa agatgttaca 720
attattttat aatgtatttt ccttagtgtt aagcttttag tatgttttaa tgtgatttta 780
tatttct 787

<210> 94
<211> 438

<212> DNA
<213> Homo sapiens

<400> 94
aaaggaaaca agttccagac tttaaataca aatgtttttc tatttcaatt ttatttcaat 60
ctcttgatat gaaatttcac aatattgtac aaaaagttat ttgttataat actgtcagat 120
tttcatctgg ttaaatgtca ttgttaggtg aaatttttat gaacaattca aatatatgtt 180
atttacaggc cacatttaaa ggctggatgg atattatgta tgcagctgtt gattcacgag 240
atgtaagtat cactcaaata ttatttatag gttctagatt tcttatggtg aatattggtg 300
gtaatttaaa cactgataca tccaaaattc tatattagaa catttaatat tgcatataaa 360
aaatgaacag tctgcttcaa tatagatgat gcttgattaa tgtgtgccta atatacaata 420
tgtagctaat atgaaacg 438

<210> 95
<211> 637
<212> DNA
<213> Homo sapiens

<400> 95
gtaaggcaca atgggaaaag agaatcaaga acaatcataa aacttgcaaa ccttcatttt 60
actagatcat actagtttta aaaaattgtt tttgtagaac aatatctcag ggtaaggcaa 120
aagtagcact gtattaagta acagcactca ataaattact gatttagtgt aagtatttat 180
agtatttttc atattattta atattttcaa tatcatttag gttaaacttc agcctgtata 240
tgaagaaaat ctgtacatgt atttatactt tgtcatcttt atcatctttg ggtcattctt 300
cactctgaat ctattcattg gtgtcatcat agataacttc aaccagcaga aaaagaagat 360
aagtattctt tagcttttac ctttcttcat tctggggttc tgtctgttaa tacagccaaa 420
taaccagaat acctgtggtc atgacagact taaatcatgt ttatattatt ttcagttgcc 480
catgtggtta tttaagctgc agggattcca gcctctagtc agtggctcct ctcaaagttt 540
atctattgga tagctttctg acccaaaaat gtgtccactc cttcggaccc atccaacggg 600
tctccagtgc tttagcttgg cttacagagc ctttcag 637

<210> 96
<211> 637
<212> DNA
<213> Homo sapiens

<400> 96
acccttgtgc ctacttttaa acatagtata atcaaattag gatcctgtag cgatcagagt 60
tttatgtacg taaggatttt gcataatatt aagatattca gaatttcaca taaatgggaa 120
aagcaggata aatgtatatg taggaggata atatccactt aaaaattaga aaagattaaa 180
ggaaagacaa atatttttg tgaaagtact attggaacac agaattgtaa ccagttttat 240
actatgtctt tactttggag gtcaagacat ctttatgaca gaggaacaga aaaaatatta 300
caatgcaatg aagaaacttg gatccaagaa acctcagaaa cccatacctc gcccagcagt 360
aagaattact tgtctccttt aatgttccaa agccatgcgt ccatatggtc aaattgagca 420
atgctctgga gcagaacata ttaggtgata tcaccaatat tgagccctaa ttataaagtt 480
catattttgc atcataattc acaacttctg cactcattag gagttaccac attccaaaaa 540

aaggaggtaa tgttctttat aatttgtgag ttgaaaactt ctagctcagg gttcctaata 600
aatacttcca aagcaaggtt cactttcctg ctaccaa 637

<210> 97
<211> 759
<212> DNA
<213> Homo sapiens

<400> 97
tatataaacc aaatatgctt tgtttagcta tataaatttt ttttccattt tttttaacat 60
gaagagaaaa aaagcacaca aaattgtttg gggtaatatg aggagggtgc acatccatcc 120
cgtatgtgga agggctttat ctacaatttt actgcattat tctttatgaa atatatatag 180
taaccttatt tctcttctct cactttctag aacaaattcc aaggaatggt ctttgatttt 240
gtaaccagac aagtctttga tatcagcatc atgatcctca tctgcctcaa catggtcacc 300
atgatggtgg aaacggatga ccagggcaaa tacatgaccc tagttttgtc ccggatcaac 360
ctagtgttca ttgttctgtt cactggagaa tttgtgctga agctcgtctc cctcagacac 420
tactacttca ctataggctg gaacatcttt gactttgtgg tggtgattct ctccattgta 480
ggtaagaaca gcttaattac caagaggtat agttacagag aaacagttgc cccaggacct 540
tctagctgat taacatggaa attaggtctg agaataataa tgcatataga tgtaaagttc 600
aacactagca tatttgaata aaaactctga aacctgggtt tattcacaaa gctaactagt 660
tagaaaccat gttaggaata ccagatttgg gaaagaggtg aagaagacag gaaataaaca 720
ttatcaggta ctctcctaat cttaaaccaa ggtcacagg 759

<210> 98
<211> 3975
<212> DNA
<213> Homo sapiens

<400> 98
aatctgtaat gctaatgcag ggagtggatc caaatattta ataaaggctc atattcataa 60
caagtttgtt gtgttcatag accttaaaaa agataaagcc atcatgtaaa gtgaaaagat 120
attatctgtt tagctgtgtt ctatgttttc cataggtatg tttctggctg agatgataga 180
aaagtatttt gtgtccccta ccttgttccg agtgatccgt cttgccagga ttggccgaat 240
cctacgtctg atcaaaggag caaaggggat ccgcacgctg ctctttgctt tgatgatgtc 300
ccttcctgcg ttgtttaaca tcggcctcct gctcttcctg gtcatgttta tctatgccat 360
ctttgggatg tccaactttg cctatgttaa aaaggaagct ggaattgatg acatgttcaa 420
ctttgagacc tttggcaaca gcatgatctg cttgttccaa attacaacct ctgctggatg 480
ggatggattg ctagcaccta ttcttaatag tgcaccaccc gactgtgacc ctgacacaat 540
tcaccctggc agctcagtta agggagactg tgggaaccca tctgttggga ttttcttttt 600
tgtcagttac atcatcatat ccttcctggt ggtggtgaac agttacatcg cggtcatcct 660
ggagaacttc agtgttgcta ctgaagaaag tgcagagccc ctgagtgagg atgactttga 720
gatgttctat gaggtttggg aaaagtttga tcccgatgcg acccagttta tagagttctc 780
taaactctct gattttgcag ctgccctgga tcctcctctt ctcatagcaa aacccaacaa 840
agtccagctt attgccatgg atctgcccat ggtcagtggt gaccggatcc actgtcttga 900
tattttattt gcctttacaa agcgtgtttt gggtgagagt ggagagatgg atgcccttcg 960
aatacagatg gaagacaggt ttatggcatc aaacccctcc aaagtctctt atgagcctat 1020

tacaaccact ttgaaacgta aacaagagga ggtgtctgcc gctatcattc agcgtaattt 1080
cagatgttat cttttaaagc aaaggttaaa aaatatatca agtaactata acaaagaggc 1140
aataaagggg aggattgact tacctataaa acaagacatg attattgaca aactgaatgg 1200
gaactccact ccagaaaaaa cagatgggag ttcctctacc acctctcctc cttcctatga 1260
tagtgtaaca aaaccagaca aggaaaagtt tgagaaagac aaaccagaaa aagaaagcaa 1320
aggaaaagag gtcagagaaa atcaaaagta aaaagaaaca aagaattatc tttgtgatca 1380
attgtttaca gcctatgaag gtaaagtata tgtgtcaact ggacttcaag aggaggtcca 1440
tgccaaactg actgttttaa caaatactca tagtcagtgc ctatacaaga cagtgaagtg 1500
acctctctgt cactgcaact ctgtgaagca gggtatcaac attgacaaga ggttgctgtt 1560
tttattacca gctgacactg ctgaggagaa acccaatggc tacctagact atagggatag 1620
ttgtgcaaag tgaacattgt aactacacca aacaccttta gtacagtcct tgcatccatt 1680
ctatttttaa cttccatatc tgccatattt ttacaaaatt tgttctagtg catttccatg 1740
gtccccaatt catagtttat tcataatgct atgtcactat ttttgtaaat gaggtttacg 1800
ttgaagaaac agtatacaag aaccctgtct ctcaaatgat cagacaaagg tgttttgcca 1860
gagagataaa atttttgctc aaaaccagaa aaagaattgt aatggctaca gtttcagtta 1920
cttccatttt ctagatggct ttaattttga aagtatttta gtctgttatg tttgtttcta 1980
tctgaacagt tatgtgcctg taaagtctcc tctaatattt aaaggattat ttttatgcaa 2040
agtattctgt ttcagcaagt gcaaatttta ttctaagttt cagagctcta tatttaattt 2100
aggtcaaatg ctttccaaaa agtaatctaa taaatccatt ctagaaaaat atatctaaag 2160
tattgcttta gaatagttgt tccactttct gctgcagtat tgctttgcca tcttctgctc 2220
tcagcaaagc tgatagtcta tgtcaattaa ataccctatg ttatgtaaat agttatttta 2280
tcctgtggtg catgtttggg caaatatata tatagcctga taaacaactt ctattaaatc 2340
aaatatgtac cacagtgtat gtgtcttttg caagcttcca acagggatgt atcctgtatc 2400
attcattaaa catagtttaa aggctatcac taatgcatgt taatattgcc tatgctgctc 2460
tattttactc aatccattct tcacaagtct tggttaaaga atgtcacata ttggtgatag 2520
aatgaattca acctgctctg tccattatgt caagcagaat aatttgaagc tatttacaaa 2580
caccttttact tttgcacttt taattcaaca tgagtatcat atggtatctc tctagatttc 2640
aaggaaacac actggatact gcctactgac aaaacctatt cttcatattt tgctaaaaat 2700
atgtctaaaa cttgcgcaaa tataaataat gtaaaaatat aatcaacttt atttgtcagc 2760
attttgtaca taagaaaatt attttcaggt tgatgacatc acaatttatt ttactttatg 2820
cttttgcttt tgatttttaa tcacaattcc aaacttttga atccataaga tttttcaatg 2880
gataatttcc taaaataaaa gttagataat gggttttatg gatttctttg ttataatata 2940
ttttctacca ttccaatagg agatacattg gtcaaacact caaacctaga tcattttcta 3000
ccaactatgg ttgcctcaat ataacctttt attcatagat gtttttttt attcaacttt 3060
tgtagtattt acgtatgcag actagtctta tttttttaat tcctgctgca ctaaagctat 3120
tacaaatata acatggactt tgttcttttt agccatgaac aaagtggcaa agttgtgcaa 3180
ttacctaaca tgatataaat ttttgttttt tgcacaaacc aaaagtttaa tgttaattct 3240
ttttacaaaa ctatttactg tagtgtattg aagaactgca tgcagggaat tgctattgct 3300
aaaaagaatg gtgagctacg tcattattga gccaaaagaa taaatttcat tttttattgc 3360
atttcactta ttggcctctg gggtttttg ttttgtttt ttgctgttgg cagtttaaaa 3420
tatatataat taataaaacc tgtgcttgat ctgacatttg tatacataaa agtttacatg 3480
aattttacaa cagactagtg catgattcac caagcagtac tacagaacaa aggcaaatga 3540
aaagcagctt tgtgcacttt tatgtgtgca aaggatcaag ttcacatgtt ccaactttca 3600
ggtttgataa taatagtagt aaccacctac aatagctttc aatttcaatt aactcccttg 3660
gctataagca tctaaactca tcttctttca atataattga tgctatctcc taattacttg 3720
gtggctaata aatgttacat tctttgttac ttaaatgcat tatataaact cctatgtata 3780
cataaggtat taatgatata gttattgaga atttatatta actttttttt caagaaccct 3840
tggatttatg tgaggtcaaa accaaactct tattctcagt ggaaaactcc agttgtaatg 3900

catattttta aagacaattt ggatctaaat atgtatttca taattctccc ataataaatt 3960
atataaggtg gctaa 3975

<210> 99
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 99
tgtgttctgc cccagtgaga ct 22

<210> 100
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 100
cttcctgctc tgcccaaact gaat 24

<210> 101
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 101
ggcgatgtaa tgtaaggtgc tgtc 24

<210> 102
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 102
gtgccttcag ttgcaattgt tcag 24

<210> 103
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 103
ttaggaattt catatgcaga ataa 24

<210> 104
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 104
tgggccattt ttcgtcgtc 19

<210> 105
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 105
gaaagacgca ttgcagaaga aaagg 25

<210> 106

<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 106
ctattggcat gtgttggtgc taca 24

<210> 107
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 107
gtgctggttt ctcatttaac tttac 25

<210> 108
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 108
ttcccaactt aatttgatat ttagc 25

<210> 109
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 109

gcagtttggg cttttcaatg ttag 24

<210> 110
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 110
gacacagttt caraatcccr aatg 24

<210> 111
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 111
ttagggctac gtttcatttg tatg 24

<210> 112
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 112
agcactgatg gaaaaccaaa ctat 24

<210> 113
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 113
agcccatgca gtaatataaa tcct 24

<210> 114
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 114
tccaggctga taagctatgt ctaa 24

<210> 115
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 115
ctgtggcctg cctgagcgta tt 22

<210> 116
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 116
ccaattctac tttttaagga aatg 24

<210> 117
<211> 19

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 117
aaatacttgt gcctttgaa 19

<210> 118
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 118
gtacatacaa tatacacaga tgc 23

<210> 119
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 119
aggcagcaga acgacttgta ata 23

<210> 120
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 120
atccggtttt aatttcataa ctca 24

<210> 121
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 121
gttgagcacc cttagtgaat aata 24

<210> 122
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 122
tcacacgctc tagactactt ctct 24

<210> 123
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 123
tgcaaatact tcagcccttt caaa 24

<210> 124
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

oligonucleotide

<400> 124
ttccccacca gactgctctt tc 22

<210> 125
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 125
gcagcaggca ggctctca 18

<210> 126
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 126
tctcccatgt tttaattttc aacc 24

<210> 127
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 127
ataatcttgc aaaatgaaat caca 24

<210> 128
<211> 19
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 128
atccgggatg acctactgg 19

<210> 129
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 129
gataacgaga gccgtagaga ttcc 24

<210> 130
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 130
agccagccat gcctgaacta 20

<210> 131
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 131
tgtttgcttg tcatattgct caa 23

<210> 132
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 132
tgcactattc ccaactcaca aa 22

<210> 133
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 133
aagggtgtct ctgtaacaaa aatg 24

<210> 134
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 134
gtgatggcca ggtcaacaaa 20

<210> 135
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 135
ctgggactgt tctccatatt ggtt 24

<210> 136
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 136
tttgcagggg ccaggaag 18

<210> 137
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 137
cattgtggga aaatagcata agc 23

<210> 138
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 138
gcaagaaccc tgaatgttag aaa 23

<210> 139
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 139
taatgctttt aagaatcata caaa 24

<210> 140
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 140
ccagcgtggg agttgacaat c 21

<210> 141
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 141
cggcatgcag ctctttggta 20

<210> 142
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 142
atgtgccatg ctggtgtatt tc 22

<210> 143
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 143
cacccatctt ctaatcacta tgc 23

<210> 144
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 144
cagcaatttg gagattattc att 23

<210> 145
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 145
gcagccactg atgatgataa 20

<210> 146
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 146
ctgccagttc ctataccact t 21

<210> 147
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 147
tacagcagaa attgggaaag at 22

<210> 148
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 148
gtattcatac ctacccacac ctat 24

<210> 149
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 149
ttcttggcag gcaacttatt acc 23

<210> 150
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 150
taagctgcac tccaaatgaa agat 24

<210> 151
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 151
ggctgaatgt ttccacaact 20

<210> 152
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 152
gttcaactat tcggaaacac g 21

<210> 153
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 153
aggcagagga aaacaatgg 19

<210> 154

<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 154
acaaggtggg ataattaaaa atg 23

<210> 155
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 155
gtttctctgc cctcctattc c 21

<210> 156
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 156
aagctacctt gaacagagac a 21

<210> 157
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 157

aatgatgatt ctgtttatta 20

<210> 158
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 158
aatttgccat tccttttg 18

<210> 159
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 159
ttgacatcga agacgtgaat aatc 24

<210> 160
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 160
ccatctgggc tcataaactt gta 23

<210> 161
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 161
ccctttgaaa attatatcag taa 23

<210> 162
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 162
atttggtcgt ttatgcttta ttc 23

<210> 163
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 163
tccagcacta aaatgtatgg taat 24

<210> 164
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 164
atttggcaga gaaaacactc c 21

<210> 165
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 165
ttttagccat ccattttcta tttt 24

<210> 166
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 166
tattttcccc catatcattt ga 22

<210> 167
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 167
tttgcaagaa actagaaagt c 21

<210> 168
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 168
ttgatgcgtg acaaaatgg 19

<210> 169
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 169
gaccagagtg aatatgtgac tacc 24

<210> 170
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 170
ctgggatgat cttgaatcta atc 23

<210> 171
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 171
gcaactcagt tcatggaatt tgaa 24

<210> 172
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

oligonucleotide

<400> 172
cttgttttcg ttttaaagta gta 23

<210> 173
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 173
caaagatcac cctggaagct cagtt 25

<210> 174
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 174
ttcaagcgca gctgcaaact gagat 25

<210> 175
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 175
acatcggcct cctactcttc cta 23

<210> 176
<211> 21
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 176
acagatgggt tcccacagtc c 21

<210> 177
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 177
taacgcatga tttcttcact ggtt 24

<210> 178
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 178
atcccaaaga tggcgtagat ga 22

<210> 179
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 179
tgagaaatag gctaaggacc tcta 24

<210> 180
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 180
cctaggggct ggattcc 17

<210> 181
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 181
aaggggtgca aacctgtgat ttt 23

<210> 182
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 182
agggccatgt ggttgccata c 21

<210> 183
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 183
cttccggttt atgttttcat ttct 24

<210> 184
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 184
tctttattag ttttgcacat ttta 24

<210> 185
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 185
caatccttcc aaggtctcct atc 23

<210> 186
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 186
tttcatcttt gccttcttgc tcat 24

<210> 187
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 187
catgtccact gcagcttgtc ca 22

<210> 188
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 188
tccccttttac acagagtcac agtt 24

<210> 189
<211> 15
<212> DNA
<213> Homo sapiens

<400> 189
gcatttgaag atata 15

<210> 190
<211> 15
<212> DNA
<213> Homo sapiens

<400> 190
gcatttgacg atata 15

<210> 191
<211> 15
<212> DNA
<213> Homo sapiens

<400> 191
atcatatcct tcctg 15

<210> 192
<211> 15
<212> DNA
<213> Homo sapiens

<400> 192
atcatatmct tcctg 15

<210> 193
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 193
atgggttgaa tgactttctg acat 24

<210> 194
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 194
aggcatttcc tgtacaggga ctac 24

<210> 195
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 195
acaggaaatg cctcttctta cttc 24

<210> 196
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 196
tttccccaag gattctacta ctgt 24

<210> 197
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 197
agtgcatgta actgacacaa tcac 24

<210> 198
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 198
cttgcgttcc tgtttgggtc tct 23

<210> 199
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 199
tccgcttctt taccagggaa tc 22

<210> 200
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 200
aggcagtgaa ggcaacttga ctaa 24

<210> 201
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 201
cagggcaata tttataaata atgg 24

<210> 202
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 202
tttggaaaat gtgtagctca ataa 24

<210> 203
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 203
aaggcatggt agtgcataaa ag 22

<210> 204
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 204
atgaaacata aagggaggtc aa 22

<210> 205
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 205
aatgtgagct tggctattgt ctct 24

<210> 206
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 206
ataggctccc accagtgatt tac 23

<210> 207
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 207
aggcccctta tatctccaac tg 22

<210> 208
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 208
caacaaggct tctgcacaaa ag 22

<210> 209
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 209
cttggtggct tgccttgac 19

<210> 210
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 210
tcatgagtgt cgccatcagc 20

<210> 211
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 211
ggaaagctga tggcgacact 20

<210> 212
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 212
ctgagacatt gcccaggtcc 20

<210> 213
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 213
tttttacccg ttgctttctt ta 22

<210> 214
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 214
tatcccttgc tctttcattt atct 24

<210> 215
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 215
gccggtaaaa tagctgttga gtag 24

<210> 216
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 216
gccattgcaa acatttattt cgta 24

<210> 217
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 217
gcgtgtttgc gctaatag 18

<210> 218

<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 218
ctaagtcact tgattcacat ctaa 24

<210> 219
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 219
acagggtggc tgaagtgttt ta 22

<210> 220
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 220
gtgggaggtg gcaggttatt 20

<210> 221
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 221

caattagcag acttgccgtt att 23

<210> 222
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 222
tctcttgagt tcggtgtttt atga 24

<210> 223
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 223
accgaactca agagaattgc tgta 24

<210> 224
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 224
aaaggaccgt atgcttgttc acta 24

<210> 225
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 225
tatgaatgcg cattttactc tttg 24

<210> 226
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 226
tggagctcaa cttagatgct actg 24

<210> 227
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 227
ggtgctggtg ggataggagt tttt 24

<210> 228
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 228
tccattaaat tctggcatat tctt 24

<210> 229
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 229
tcagaggggt gctttcttcc acat 24

<210> 230
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 230
cttcggctgt cattgtcctc aaag 24

<210> 231
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 231
gcaaaggaca ttggctctga gaat 24

<210> 232
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 232
ctgcctgcac cagtcacaac tct 23

<210> 233
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 233
tgggctttgc tgctttcaa 19

<210> 234
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 234
agtaactgtg acgcaggact ttta 24

<210> 235
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 235
ccctgttcct ccagcagatt a 21

<210> 236
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

oligonucleotide

<400> 236
gtgatggcca ggtcaacaaa 20

<210> 237
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 237
tttgatttgg gactgttgta aac 23

<210> 238
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 238
aaggcaatta taaactcttt caag 24

<210> 239
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 239
tgggagttaa attaagttgc tcaa 24

<210> 240
<211> 24
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 240
acattttatg aacactccca gtta 24

<210> 241
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 241
attaacactg ttcttgcttt tat 23

<210> 242
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 242
gtgccagcgt gggagttc 18

<210> 243
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 243
gtgggggctc taggaaacct 20

<210> 244
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 244
tttaatgaaa atgaggaaaa tgtt 24

<210> 245
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 245
gaccaagcat ttttatttca ttc 23

<210> 246
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 246
agtggcagca agattgtca 19

<210> 247
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 247
ggccttgctt ttgagttcc 19

<210> 248
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 248
ggtctttgcc tatttctatg gtg 23

<210> 249
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 249
ttaaaccgct tgaagatcta aata 24

<210> 250
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 250
tatacaccaa aatatctcct tat 23

<210> 251
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 251
ggggcacacc taattaattt ttat 24

<210> 252
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 252
aaagaggata ctcaagacca cata 24

<210> 253
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 253
cccaccaaca caaatatacc taat 24

<210> 254
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 254
tgaagggaaa gggaaaagat tt 22

<210> 255
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 255
tccagcctta ggcacctgat aa 22

<210> 256
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 256
ataaagcagc aaagtgcagc atac 24

<210> 257
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 257
aaggctgaac tgtgtagaca tttt 24

<210> 258
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 258
tgacatttcc atggtacaaa gtgt 24

<210> 259
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 259
tttgttgttg gcttttcact tat 23

<210> 260
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 260
ccacctggca gtttgattg 19

<210> 261
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 261
taagcgtggt caacaactac agt 23

<210> 262
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 262
attcttgcca gcatttattg tc 22

<210> 263
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 263
caaaacattg ccccaaaag 19

<210> 264
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 264
tcaaactaaa caatttccct ctaa 24

<210> 265
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 265
gataattaaa aactcactga tgta 24

<210> 266

<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 266
ggaggctaaa ggaaagagta tg 22

<210> 267
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 267
attttatagc cagcaaagaa cac 23

<210> 268
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 268
ctagaaattc gggctgtgaa 20

<210> 269
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 269

ctgctttgtg acctaaggca agtt 24

<210> 270
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 270
gtgaccatgt taaggcagat gagg 24

<210> 271
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 271
ggaatggtct ttgattttgt aacc 24

<210> 272
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 272
tccttaactg aataaaagca cctc 24

<210> 273
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 273
tggaacaccc atcaaagaag atact 25

<210> 274
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 274
gtgggagtcc tgttgacaca aac 23

<210> 275
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 275
agcgattcat ggcatcaaac 20

<210> 276
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 276
acgtggtgga aggcgtcata 20

<210> 277
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 277
gcgacccagt ttatagagtt tgcc 24

<210> 278
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 278
cttgtttgcg tttcaacgtg gtc 23

<210> 279
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 279
caaagatcac cctggaagct cagtt 25

<210> 280
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 280
atccagggca tctgcaaaat cagaa 25

<210> 281
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 281
tgcctatgtt aagagggaag ttggg 25

<210> 282
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 282
atgaccgcga tgtacatgtt cag 23

<210> 283
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 283
tcaattgttt acagcccgtg atg 23

<210> 284
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

oligonucleotide

<400> 284
tttatacaaa ggcagacaac at 22

<210> 285
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 285
aggcgtaatg gctactcaga cga 23

<210> 286
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 286
gtaatccctc tccccgaaca taaac 25

<210> 287
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 287
tttgattcac gggttgttta ctctta 26

<210> 288
<211> 26
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 288
ttctatggaa catttacagg cacatt 26

<210> 289
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 289
taatgtgcct gtaaatgttc cataga 26

<210> 290
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 290
caggcttctt agaaaggact gatagg 26

<210> 291
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 291
gtcccagcag catgactatc 20

<210> 292
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 292
cccactgggt aaaattacta ac 22

<210> 293
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 293
tagccatctt ctgctcttgg t 21

<210> 294
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 294
tggcttccca tattagactt ctg 23

<210> 295
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 295
tcttgcctat gctgctgtat ctta 24

<210> 296
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 296
agtcgggctt ttcatcattg ag 22

<210> 297
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 297
ttcttcatgt cattaagcaa tagg 24

<210> 298
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 298
ttcaatttaa aagtgctagg aaca 24

<210> 299
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 299
cttcaggtgg atgtcacagt cacta 25

<210> 300
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 300
attcaagcaa tgccaagagt atca 24

<210> 301
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 301
ctttcaatag taatgcctta tcat 24

<210> 302
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 302
tcctgcatgc atttcaccaa c 21

<210> 303
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 303
ctgttcacat tttgtaaaac taat 24

<210> 304
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 304
atcccaaaga tggcgtagat ga 22

<210> 305
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 305
cacgctgctc tttgctttga 20

<210> 306
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 306
gatctttgtc agggtcacag tct 23

<210> 307
<211> 9
<212> DNA
<213> Homo sapiens

<400> 307
tacaaagaa 9

<210> 308
<211> 9
<212> DNA
<213> Homo sapiens

<400> 308
tacagagaa 9

<210> 309
<211> 9
<212> DNA
<213> Homo sapiens

<400> 309
tacagagaa 9

<210> 310
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 310
tgtgtccgcc agtagatgg 19

<210> 311
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 311
tttttgacca cagaggttta caa 23

<210> 312
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 312
gaagcggagg cataagcaga 20

<210> 313
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 313
ggtgcagata atgaaatgtt ttgt 24

<210> 314
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 314
caccctatg ccaaatgtca aaga 24

<210> 315
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 315
caaaaacaaa cttataccca gaag 24

<210> 316
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 316
caaatattgg gcaaacccta at 22

<210> 317
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 317
aaggtgccat cacaaaatca t 21

<210> 318
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 318
atcgcttgct ttcctaactc ttgt 24

<210> 319
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 319
aagtcactat ttggctttgg ttg 23

<210> 320
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 320
agaagcccaa aaaggaacaa gata 24

<210> 321
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 321
ggcccagaaa agtatattac agtt 24

<210> 322
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 322
tccttaaata agcccatgtc taat 24

<210> 323
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 323
tctcaaagaa attttacaga tact 24

<210> 324
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 324
aatggccatg gtaacctact aaca 24

<210> 325
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 325
caggctatac ccacaaggag att 23

<210> 326

<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 326
tgttaatttt ggcttggatg tt 22

<210> 327
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 327
tcactccttt gcgcttatca a 21

<210> 328
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 328
agggctctat gtgccaaacc 20

<210> 329
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 329

aggggcctac taccttacac cag 23.

<210> 330
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 330
tgtaatccca ggtaagaaga aac 23

<210> 331
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 331
taccgggatg aactgtaata ataa 24

<210> 332
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 332
ttctggcact cttcctcagg taac 24

<210> 333
<211> 22
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 333
gtcccatttg aatccattgt gc 22

<210> 334
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 334
ggcccccaag cgattctg 18

<210> 335
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 335
tgtacaccca cagtctcaac tatt 24

<210> 336
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 336
acagccacct ttgtaaataa 20

<210> 337
<211> 20

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 337
tttttcgcaa agagttctat 20

<210> 338
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 338
aaactgaccc tacctccatt tctc 24

<210> 339
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 339
actcagccta tgcttttcat ttca 24

<210> 340
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 340
cagatattta tttggggaca ttat 24

<210> 341
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 341
aaatctttgc ktttatcact cagt 24

<210> 342
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 342
tagtgcctgg ctttgtttta tgac 24

<210> 343
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 343
cggatttggg aaagctgtct ct 22

<210> 344
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

oligonucleotide

<400> 344
agagcacctt gaaggaaaca acaa 24

<210> 345
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 345
tccctcaact gaagtacaga tagt 24

<210> 346
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 346
ataattgcgt tcttccccta ccc 23

<210> 347
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 347
aagccctggc accatcctg 19

<210> 348
<211> 20
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 348
tttgcaaaga aatgctatgt 20

<210> 349
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 349
ctgggtaaca gacttcagta at 22

<210> 350
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 350
atgggattgt cttctcaagt ttct 24

<210> 351
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 351
gatggcaaga tcaacaaatg ga 22

<210> 352
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 352
cttgatctgg gactgctgtg atg 23

<210> 353
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 353
aggatataat ttttggttca aca 23

<210> 354
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 354
ttttcagtgc tcttgatagt agtg 24

<210> 355
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 355
gtgccaatga gcgacagg 18

<210> 356
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 356
ccacgtgtgg ttctatgata cc 22

<210> 357
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 357
accgtgggag cgtacagtca 20

<210> 358
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 358
cggcatgcag ctctttggta 20

<210> 359
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 359
tggccacgtt cctagctact gtc 23

<210> 360
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 360
gagttccctt tttaggctgt tatt 24

<210> 361
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 361
tcttattgcc ttcatggatt tcta 24

<210> 362
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 362
tgaaaaataa gatgcgggag tg 22

<210> 363
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 363
gtgaggctgg ggttgtttat g 21

<210> 364
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 364
gagatgggaa tggaaccacc a 21

<210> 365
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 365
ttcgataatg catataagca caa 23

<210> 366
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 366
aaggggaaa atcacatctt t 21

<210> 367
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 367
ttaaatgagg catattcagt ctcc 24

<210> 368
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 368
ggaagtggag tggggaagg 19

<210> 369
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 369
attcttgcca atatgcattt cact 24

<210> 370
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 370
ttcttttgta ctcactatta tactaa 26

<210> 371
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 371
aaacttgcct cttttaaaaa caat 24

<210> 372
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 372
taccacaccc tataccttca gtca 24

<210> 373
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 373
gagtatggca ccctttttcta tcta 24

<210> 374

<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 374
gctatgttcc cctcgctgtc t 21

<210> 375
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 375
tgcttgccaa gagcctgac 19

<210> 376
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 376
gctggcaagt tctaccactg tg 22

<210> 377
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 377

caaacgaaga acatcaggga aata 24

<210> 378
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 378
ttcacaatat tgtacaaaaa gtta 24

<210> 379
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 379
attaccacca atattcacca taag 24

<210> 380
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 380
tcagggtaag gcaaaagtag cac 23

<210> 381
<211> 24
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 381
gaaccccaga atgaagaaag gtaa 24

<210> 382
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 382
tttgtgaaag tactattgga acac 24

<210> 383
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 383
acgcatggct ttggaacat 19

<210> 384
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 384
cccgtatgtg gaagggcttt at 22

<210> 385
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 385
ctaggttgat ccgggacaaa acta 24

<210> 386
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 386
aacggatgac cagggcaaat ac 22

<210> 387
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 387
ctagaaggtc ctggggcaac tg 22

<210> 388
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 388
aagccatcat gtaaagtgaa aag 23

<210> 389
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 389
atcccaaaga tggcatagat a 21

<210> 390
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 390
cacgctgctc tttgctttga 20

<210> 391
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 391
tgagctgcca gggtgaattg 20

<210> 392
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic

oligonucleotide

<400> 392
ttgctagcac ctattcttaa tagtgc 26

<210> 393
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 393
ccagggcagc tgcaaaatca gag 23

<210> 394
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 394
cccgatgcga cccagttta 19

<210> 395
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 395
tggaggggtt tgatgccata 20

<210> 396
<211> 23
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 396
gatggatgcc cttcgaatac aga 23

<210> 397
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 397
ttcccattta gtttgtcaat aatc 24

<210> 398
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 398
aaggggagga ttgacttacc tat 23

<210> 399
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: synthetic oligonucleotide

<400> 399
ttggcatgga cctcctcttg a 21

<210> 400
<211> 18
<212> DNA
<213> Homo sapiens

<400> 400
caagataatg atgatgag 18

<210> 401
<211> 15
<212> DNA
<213> Homo sapiens

<400> 401
caagatgatg atgag 15

<210> 402
<211> 13
<212> DNA
<213> Homo sapiens

<400> 402
tggtgtaagg tag 13

<210> 403
<211> 13
<212> DNA
<213> Homo sapiens

<400> 403
tggtataagg tag 13

<210> 404
<211> 17
<212> DNA
<213> Homo sapiens

<400> 404
ccccttatat ctccaac 17

<210> 405
<211> 17

<212> DNA
<213> Homo sapiens

<400> 405
ccccttatay ctccaac 17

<210> 406
<211> 15
<212> DNA
<213> Homo sapiens

<400> 406
aaatacgtaa tcgat 15

<210> 407
<211> 15
<212> DNA
<213> Homo sapiens

<400> 407
aaatacataa tcgat 15

<210> 408
<211> 15
<212> DNA
<213> Homo sapiens

<400> 408
aaatacrtaa tcgat 15

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 May 2001 (31.05.2001)

PCT

(10) International Publication Number
WO 01/38564 A3

(51) International Patent Classification[7]: C12Q 1/68, A61P 43/00, C07K 14/705

(21) International Application Number: PCT/CA00/01404

(22) International Filing Date:
24 November 2000 (24.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/167.623 26 November 1999 (26.11.1999) US

(71) Applicant *(for all designated States except US)*: **MCGILL UNIVERSITY** [CA/CA]; 3550 University Street, Montreal, Quebec H3A 3V9 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ROULEAU, Guy, A.** [CA/CA]; Appartement 7, 4850 Côte Saint-Luc, Montréal, Québec H3W 2H2 (CA). **LAFRENIERE, Ronald, G.** [CA/CA]; 1264 Osborne Avenue, Verdun, Quebec H4H 1X5 (CA). **ROCHEFORT, Daniel** [CA/CA]; 2134 de Calmar, Laval, Quebec H7M 5T1 (CA). **COSSETTE, Patrick** [CA/CA]; 3550 University Street, Montreal, Quebec H3A 3V9 (CA). **RAGSDALE, David** [CA/CA]; 3550 University Street, Montreal, Quebec H3A 3V9 (CA).

(74) Agents: **DUBUC, Jean, H.** et al.; Goudreau Gage Dubuc, The Stock Exchange Tower, Suite 3400, 800 Place Victoria, P.O. Box 242, Montreal, Quebec H4Z 1E9 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
8 November 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/38564 A3

(54) Title: LOCI FOR IDIOPATHIC GENERALIZED EPILEPSY, MUTATIONS THEREOF AND METHOD USING SAME TO ASSESS, DIAGNOSE, PROGNOSE OR TREAT EPILEPSY

(57) Abstract: The present invention relates to epilepsy. More particularly, the present invention relates to idiopathic generalized epilepsy (IGE) and to the identification of three genes mapping to chromosome 2, which show mutations in patients with epilepsy. The invention further relates to nucleic acid sequences, and protein sequences of these loci (SCNA) and to the use thereof to assess, diagnose, prognose or treat epilepsy, to predict an epileptic individual's response to medication and to identify agents which modulate the function of the SCNA. The invention provides screening assays using SCN1A, SCN2A and/or SCN3A which can identify compounds which have therapeutic benefit for epilepsy and related neurological disorders. In a particular embodiment, the invention provides a method for identifying, from a library of compounds, a compound with therapeutic effect on epilepsy or other neurological disorders comprising: providing a screening assay comprising a measurable biological activity of SCN1A, SCN2A or SCN3A protein or gene; contacting this screening assay with a test compound; and detecting if the test compound modulates the biological activity of SCN1A, SCN2A or SCN3A protein or gene; wherein a test compound which modulates the biological activity thereof is a compound with the desired therapeutic effect.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/01404

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 A61P43/00 C07K14/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOULARD BRUNO ET AL: "Identification of a new locus for generalized epilepsy with febrile seizures plus (GEFS+) on chromosome 2q24-q33." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 65, no. 5, November 1999 (1999-11), pages 1396-1400, XP002170644 ISSN: 0002-9297 the whole document ---	1-13
X	BAULAC S ET AL: "A second locus for familial generalized epilepsy with febrile seizures plus maps to chromosome 2q21-q33." AMERICAN JOURNAL OF HUMAN GENETICS, (1999 OCT) 65 (4) 1078-85. , XP002170645 the whole document ---	1-13
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2001	11/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Reuter, U

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUGSLEY MICHAEL K ET AL: "Effects of bisaramil, a novel class I antiarrhythmic agent, on heart, skeletal muscle and brain Na+ channels." EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 342, no. 1, 19 January 1998 (1998-01-19), pages 93-104, XP001009949 ISSN: 0014-2999 the whole document	12,13
A	WALLACE ROBYN H ET AL: "Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel beta1 subunit gene SCN1B." NATURE GENETICS, vol. 19, no. 4, August 1998 (1998-08), pages 366-370, XP001009923 ISSN: 1061-4036 cited in the application the whole document	1-13
A	MALO M S ET AL: "TARGETED GENE WALKING BY LOW STRINGENCY POLYMERASE CHAIN REACTION: ASSIGNMENT OF A PUTATIVE HUMAN BRAIN SODIUM CHANNEL GENE (SCN3A) TO CHROMOSOME 2Q24-31" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 91, no. 8, 12 April 1994 (1994-04-12), pages 2975-2979, XP002051362 ISSN: 0027-8424 the whole document	1-13
A	MALO M S ET AL: "LOCALIZATION OF A PUTATIVE HUMAN BRAIN SODIUM CHANNEL GENE (SCN1A) TO CHROMOSOME BAND 2Q24" CYTOGENETICS AND CELL GENETICS,CH,BASEL, vol. 67, no. 3, 1994, pages 178-186, XP000603748 ISSN: 0301-0171 the whole document	1-13
A	PLUMMER NICHOLAS W ET AL: "Evolution and diversity of mammalian sodium channel genes." GENOMICS, vol. 57, no. 2, 15 April 1999 (1999-04-15), pages 323-331, XP002170646 ISSN: 0888-7543 the whole document	1-13

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 21875 A (UNIV UTAH RES FOUND) 6 May 1999 (1999-05-06) the whole document ---	1-13
P,X	ESCAYG ANDREW ET AL: "Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2." NATURE GENETICS, vol. 24, no. 4, April 2000 (2000-04), pages 343-345, XP001009967 ISSN: 1061-4036 cited in the application the whole document -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 00/01404

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921875 A	06-05-1999	EP 1037900 A	27-09-2000